

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS,) Trial Volume 1
CORPORATION,)
)
)
Plaintiff,)
)
) C.A. No. 11-1077-RGA
v.)
)
)
PAR PHARMACEUTICAL, INC.,)
)
)
Defendants.)

Thursday, May 1, 2014
8:10 a.m.

844 King Street
Wilmington, Delaware

BEFORE: THE HONORABLE RICHARD G. ANDREWS
United States District Court Judge

APPEARANCES:

McCARTER & ENGLISH, LLP
BY: DANIEL M. SILVER, ESQ.

-and-

FITZPATRICK CELLA HARPER & SCINTO
BY: NICHOLAS N. KALLAS, ESQ.
BY: CHARLOTTE JACOBSEN, ESQ.
BY: DOMINICK A. CONDE, ESQ.
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BY: CHRISTOPHER LOH, ESQ.

Counsel for the Plaintiff

1 APPEARANCES CONTINUED:

2

3 RICHARDS LAYTON & FINGER, P.A.
4 BY: STEVEN J. FINEMAN, ESQ.

5

-and-

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LATHAM & WATKINS, LLP
6 BY: DANIEL G. BROWN, ESQ.
7 BY: JENNIFER KOH, ESQ.
7 BY: ROGER CHIN, ESQ.

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Counsel for the Defendant

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1 THE CLERK: All rise.

2 THE COURT: Good morning. Please be
3 seated.

4 I just wanted to come out and see if
5 there was anything we need to deal with before
6 our official start.

7 Mr. Silver.

8 MR. SILVER: Good morning. I'd
9 offer to make introductions if Your Honor wants,
10 but I think Your Honor knows all the relevant
11 players.

12 THE COURT: I think I know all the
13 people. I'm not sure of you, sir.

14 MR. CHIN: Roger chin.

15 THE COURT: Roger Chin. I think
16 I've heard you on the phone. Maybe I met you in
17 person, too.

18 Everyone else, I think I recognize.
19 Anything else?

20 Mr. Fineman.

21 MR. FINEMAN: Good morning, Your
22 Honor.

23 THE COURT: Good morning.

24 MR. FINEMAN: There are a few, at

1 least one major housekeeping issues we'd like to
2 take up from the start. Certain of the documents
3 that are going to be used today were produced by
4 3M Company.

5 THE COURT: Okay.

6 MR. FINEMAN: And they are
7 designated highly confidential in the Protective
8 Order. And I believe --

9 THE COURT: Okay. So I'm
10 sympathetic to keeping 3M's products, since
11 they're not actually a party here. How would you
12 like to handle this?

13 MR. FINEMAN: We've come up with a
14 couple different ways, Your Honor. One of the
15 documents that would be used is what is known as
16 the DMF. The DMF contains trade secrets and very
17 very confidential information, as I understand
18 it.

19 We spoke with Novartis last night
20 and I believe the parties are in contextual
21 agreement. I believe 3M is in agreement that for
22 the DMF, what we're going to do is we're going to
23 use a redacted version as the actual trial
24 exhibit.

1 THE COURT: Okay.

2 MR. FINEMAN: Neither party will
3 argue at any point that it's an incomplete
4 document or that both parties get the opportunity
5 to put in those pages that they believe they
6 need. We'll redact the rest.

7 And if Your Honor is okay with that.

8 THE COURT: I'm okay with that if
9 the parties are.

10 Mr. Silver.

11 MR. SILVER: That's fine, Your
12 Honor.

13 THE COURT: All right. That's good.

14 MR. FINEMAN: Now, even though we do
15 that, that will protect some of the trade
16 secrets. But even the remaining pages, we will
17 need to close the courtroom or at least ask Your
18 Honor to close the courtroom while that document
19 is being discussed.

20 THE COURT: How much discussion of
21 that document do you expect to have occur?

22 MR. FINEMAN: From our side, Your
23 Honor, not much. It will probably be under 15
24 minutes.

1 THE COURT: Is it something -- I
2 kind of vaguely remember. I might be getting one
3 trial mixed up with another trial. Yeah, I
4 probably am.

5 Is it possible that whatever is
6 being shown on, I guess, the screen can just be
7 sort of tilted toward me and -- because I really,
8 if at all, prefer not to close the courtroom.

9 MR. FINEMAN: Your Honor, we
10 certainly understand and we are cognizant of
11 that. And we tried to make arrangements for this
12 and what we're proposing is that we only close
13 the courtroom when we're discussing the DMF
14 because that's the, if you will, the crown jewels
15 of the trade secret.

16 So we want to close the courtroom
17 just for that limited period. We might even make
18 it less than ten minutes, a very short period of
19 time.

20 There will be other documents which
21 are similarly designated, but we've spoken to --
22 3M, Your Honor, is present in the courtroom and
23 is represented by Mr. McCann, so that he's able
24 to speak.

1 THE COURT: All right. I know Mr.
2 McCann.

3 MR. FINEMAN: So if they want to
4 speak for themselves, Your Honor, they certainly
5 can. But as I understand it, what we'll do with
6 the rest of the documents is we won't ask Your
7 Honor to close the courtroom. But we will not
8 publish on the screen the documents while they're
9 being used. And we'd like to reserve the right,
10 Your Honor, to redact the transcript.

11 THE COURT: Well, why don't I -- you
12 don't even have to reserve the right to redact
13 the transcript. If you mean reserve the right to
14 ask to have the transcript redacted, yeah, you
15 got that one, whether you reserve it or not.
16 Whether or not -- I mean, I think -- I hope that
17 everyone knows that I hate to do that.

18 So that, you know, the best thing is
19 if you can avoid littering the transcript with
20 stuff that 3M rightfully regards as secret.

21 Then the second best thing is
22 because 3M is actually not a party, you know.
23 There's not that much they can do to prevent what
24 you all say so I would be more sympathetic to

1 either 3M itself or to you later on or some
2 combination, but remembering that it is a public
3 trial and there is a value to redacting as little
4 as possible.

5 MR. FINEMAN: That's right, Your
6 Honor. And the three parties have tried to
7 coordinate --

8 THE COURT: Right. And I do
9 appreciate that.

10 MR. FINEMAN: That's how we propose
11 to address --

12 THE COURT: When do you think this
13 closing of the courtroom is because I see, you
14 know, maybe twenty people sitting behind the
15 bench, I have no idea who they are. I know a lot
16 of them are associated with one or the other
17 side. I guess what I'm wondering is how do I
18 actually close the courtroom? Do I require that
19 anyone that you all don't vouch for identify
20 themselves or what?

21 MR. FINEMAN: Yes, Your Honor, the
22 DMF was designated outside counsel only, I
23 believe, Your Honor, and someone in this room
24 will correct me if I'm wrong, I don't think the

1 parties to this case have had access to this
2 information, it's outside counsel.

3 THE COURT: So basically what you're
4 saying is people sitting at the table, everyone
5 else except for the person on the computers
6 leaves.

7 MR. FINEMAN: I think that's right,
8 Your Honor, and we would as I said be very
9 studious to let Your Honor know precisely when we
10 need to close it and when we need to open it and
11 minimize any disruption and minimize the absence
12 of the public to the proceedings.

13 THE COURT: Okay. Is there anyone
14 in the courtroom who objects to this?

15 All right. We'll do that. And if
16 you can, do you have an idea of when in the
17 proceedings that might be?

18 MR. FINEMAN: Your Honor, I can't
19 speak for whether Novartis is going to use it.
20 From our side I think at the earliest it will
21 come up late in the afternoon today.

22 THE COURT: Okay. Well, all right.
23 Well, in any event, Mr. Silver, do you have
24 anything to add on that.

1 MR. SILVER: No, Your Honor. We'll
2 confer to see when we need to be prepared to
3 close the courtroom.

4 THE COURT: Okay. All right. Well,
5 I will do that upon request and again, we just
6 ask that you all in the first instance be
7 judicious in what you're requesting.

8 MR. FINEMAN: Absolutely, Your
9 Honor.

10 THE COURT: All right. And
11 Mr. McCann, does 3M have anything to add?

12 MR. McCANN: Not at this time, Your
13 Honor.

14 THE COURT: When we close the
15 courtroom for this portion, does that mean that
16 Mr. McCann or somebody associated with him stays
17 or does he leave, too?

18 MR. FINEMAN: You know we have no
19 objection to the representative from 3M or their
20 counsel staying because it's, in fact, their
21 confidential information.

22 THE COURT: I just wanted to make
23 sure we're all on the same page there.

24 All right. Anything else?

1 MR. FINEMAN: Your Honor, the second
2 issue is we had last night what I would call a
3 significant difference of opinion regarding
4 objections to deposition designations, and the
5 propriety of certain counter-designations. I
6 participated in the meet and confer last night
7 myself, Your Honor, and tried to work it out. We
8 were unsuccessful.

9 I understand from counsel they would
10 like to speak to us at lunch today in a further
11 effort. My concern, Your Honor, is these
12 deposition designations in all likelihood will be
13 played this afternoon and we would like to work
14 it out and play the clips. We're happy as
15 always, Your Honor, to try to work this out. How
16 would you like to address this at this juncture?

17 THE COURT: How much volume are you
18 talking about?

19 MR. FINEMAN: Your Honor, the number
20 of objections to the number of designations was
21 overwhelming. It was frankly incredible, Your
22 Honor. Some of the designations had as many as
23 seven or eight different objections, so it's
24 tremendous.

1 THE COURT: Okay. And so the
2 objections are to the so to speak the underlying
3 forms of the question or are they to relevance or
4 to what?

5 MR. FINEMAN: Your Honor, they cover
6 the broad spectrum. It almost looks like a law
7 school hypothetical with how many objections are
8 lodged.

9 THE COURT: All right. Do you have
10 a proposal, Mr. Fineman?

11 MR. FINEMAN: Your Honor, it's their
12 objections, their objections to our testimony, so
13 if they would like to maintain objections, as of
14 last night, I specifically asked are they going
15 to drop any of the objections. Their response
16 was no, they are pressing all their objections.

17 I would ask, Your Honor, that they
18 argue their objections and then get charged with
19 the time. We'll meet with them, I'm happy to
20 discuss with them, I'll meet with them right now
21 after we're done. The second issue --

22 THE COURT: I'm sorry, the second
23 issue.

24 MR. FINEMAN: The second issue, Your

1 Honor, and again, this is something we can talk
2 about, but I want to flag it for Your Honor so
3 it's not a surprise, it is they have
4 counter-designated and a fair amount of their
5 counter-designations were not in the pretrial
6 order and they were required to be in the
7 pretrial order. There is a good cause standard
8 for why they could be added. I asked what the
9 basis was last night. There was no good cause,
10 Your Honor. And we can try to address this, but
11 this is something I want to flag with Your Honor
12 because this is going to come up today.

13 THE COURT: Thank you, Mr. Fineman.

14 Mr. Silver.

15 MR. SILVER: Your Honor, I hate to
16 take up time arguing over things that can likely
17 be resolved this morning. I would suggest that
18 we meet and confer at the first break in the
19 trial and if issues are still lingering at that
20 point we can bring that to Your Honor's
21 attention. There are several objections that we
22 consider to be valid. We are going to trim those
23 down a little. Mr. Fineman says there were not
24 in the pretrial order. We'll take a look at that

1 and hope to resolve that issue as well.

2 THE COURT: Okay. It seems like
3 there is probably not a whole lot I can do about
4 it right now, so having you all try to narrow
5 down what's in dispute seems like a productive
6 use of my time.

7 Okay. So anything else?

8 MR. FINEMAN: That's all from our
9 side, Your Honor.

10 THE COURT: Mr. Silver.

11 MR. SILVER: That's it for us, Your
12 Honor.

13 THE COURT: So we'll take a roughly
14 ten-minute recess and come back and be prepared
15 to start.

16 All right.

17 MR. SILVER: Thank you, Your Honor.

18 THE COURT: Thank you.

19 (A brief recess was taken.)

20 THE CLERK: All rise.

21 THE COURT: All right. Good
22 morning.

23 Let's be seated. Are we prepared to
24 proceed?

1 MR. SILVER: Your Honor, one more
2 housekeeping issue that was just brought to my
3 attention. I apologize.

4 The defendants do have one fact
5 witness present that we would ask him to be
6 sequestered until he testifies.

7 THE COURT: All right. And I take
8 it there's no objection to that?

9 MR. BROWN: None, Your Honor.

10 THE COURT: All right. So is the
11 witness sequestered?

12 MR. BROWN: He's not here.

13 MR. FINEMAN: Who is he?

14 THE COURT: Well, even better.

15 All right. So go ahead.

16 Ms. Jacobsen.

17 MS. JACOBSEN: Good morning, Your
18 Honor. I have some books of slides.

19 May I approach?

20 THE COURT: Sure.

21 MS. JACOBSEN: Your Honor, Par seeks
22 approval from the FDA to market three
23 Rivastigmine transdermal products.

24 For the purposes of Your Honor's

1 infringement analysis, there's no difference
2 between their products. They contain the same
3 ingredients and they're just simply different
4 size patches that deliver different size doses of
5 Rivastigmine.

6 The only claim at issue is Claim 7
7 of the '031 patent. As Your Honor is aware, the
8 claims of the '031 patent fall into two
9 categories. The first category requires proof
10 that the accused product contain an amount of
11 antioxidant that functions to significantly
12 reduce oxidative degradation over a prolonged
13 period of time in the accused product.

14 And those are the function claims.
15 And they're not at issue in this case.

16 The second category of claims
17 require an affirmative proof that the presence of
18 an antioxidant, but not affirmative proof that
19 it's functioning as such in the accused product
20 for there to be a finding of infringement.

21 And those are the presence claims.
22 And Claim 7 of the '031 patent, the claim at
23 issue, is a presence claim.

24 So with respect to infringement of

1 Claim 7, there are two questions. The first: Is
2 acetaldehyde an antioxidant? That is, is it an
3 agent that reduces objection day active
4 degradation?

5 The second question is: Do Par's
6 ANDA products contain about 0.01 to about 0.5
7 percent by weight of acetaldehyde? And, Your
8 Honor, we will present evidence, and of course it
9 is our burden to prove infringement by a
10 preponderance of the evidence, that the answer to
11 both of those questions is yes.

12 Now, I'll start with the second
13 question, because as Your Honor observed at the
14 pretrial conference, there's really no factual
15 dispute here. The controlling case is a Federal
16 Circuit decision in Sunovion. And in Sunovion,
17 if an ANDA filer seeks FDA approval to market a
18 generic product that falls within the scope of a
19 valid claim, it's an act of infringement as a
20 matter of law.

21 So how then does the court determine
22 whether Par is seeking approval to manufacture a
23 generic product that falls within the scope of
24 Claim 7 of the '031 patent? Well, according to

1 the Federal Circuit in the Sunovion, it's by
2 looking at the ANDA specification. Because that
3 describes the product that Par is asking for
4 approval to manufacture and sell. It's
5 essentially the blueprint for their products.

6 Par concedes that its ANDA
7 specification commits its ANDA products to
8 contain not more than 1,000 part per million of
9 acetaldehyde. One thousand parts per million is
10 0.1 percent of acetaldehyde.

11 And that means that if Par's's ANDA
12 products are approved, Par will be permitted to
13 make a product with anywhere between 0 and 0.1
14 percent of acetaldehyde. So if we now compare
15 Par's specification with the '031 patent, we can
16 see that 90 percent of Par's ANDA specification,
17 that's between 0.1 and -- 0.01 and 0.1 fall
18 within the claims range. And that's without even
19 considering the scope of the claims are about.

23 Par will allege that it uses an
24 adhesive that has undergone a rigorous washing

1 process that minimizes the amount of acetaldehyde
2 in its adhesive. So Par argues that even though
3 its ANDA specification permits it, it won't
4 actually make a product with an amount of
5 acetaldehyde that falls within the claim numeric
6 range.

7 But in Sunovion, the Federal Circuit
8 rejected what the Court called "but I won't do
9 it" defense. And that's at 731 F.3rd at 1218.

10 And that's once this case is over,
11 there will be nothing to stop Par from going out
12 and making that washing process less rigorous,
13 less time consuming or less expensive and making
14 a product with a hundred, 500, or even a thousand
15 parts per million of acetaldehyde. And that's
16 entirely acceptable given Par's ANDA
17 specification, but it's not permissible and it's
18 not acceptable given the '031 patent. And that's
19 because all of those amounts fall within the
20 claimed numeric range.

21 The plaintiffs should not have to go
22 out and test a product that Par actually puts on
23 the market to determine whether or not to bring a
24 second infringement action.

1 The Federal Circuit explained in
2 Sunovion that the Hatch Waxman Act made filing an
3 ANDA a technical act of infringement precisely so
4 that infringement disputes were resolved before
5 approved.

6 Now, Your Honor, at the pretrial
7 conference Par argued that Sunovion was
8 distinguishable because the FDA in that case had
9 mandated infringement. And, Your Honor, that's
10 not right.

11 The patents claim in issue in
12 Sunovion required that the drug contain not more
13 than 0.25 percent of a particular impurity. The
14 FDA had requested that the ANDA filing in
15 Sunovion narrow its specification to provide for
16 not more than 0.3 percent. But even the FDA's
17 range allowed for amounts outside of the claimed
18 range and those are the amounts from 0.25 to 0.3
19 percent.

20 Now, in fact, the ANDA filer hadn't
21 done that, they amended their specification to
22 allow for not more than 0.6 percent, and they
23 said the ANDA specification provided that the
24 product could contain between 0 and 0.6 percent

1 of the impurity.

2 And the ANDA filer had actually
3 represented that all of its products would
4 contain more than 0.3 percent of impurity, so
5 everything that it made would have between 0.3
6 and 0.6 percent of that impurity and none of them
7 would have less than .25, which was what was
8 required by the claim.

9 And nevertheless, the Federal
10 Circuit found infringement as a matter of law
11 because the ANDA specification included products
12 with an amount of impurity that fell within the
13 claimed range, and that's exactly the case here.
14 Par's ANDA specification includes products with
15 amounts of acetaldehyde that fall within the
16 claimed range.

17 And during the pretrial conference,
18 Par also argued that the controlling case was
19 Glaxo v. Novopharm and that in this case, as in
20 that case, Your Honor should consider the ANDA
21 batch products.

22 The Federal Circuit explained in
23 Sunovion that reference to actual samples of a
24 generic composition in Glaxo was necessary

1 because the ANDA specification itself did not
2 resolve the question of infringement in the first
3 instance.

4 And that's at 731 F.3rd at 1279 to
5 80. And here is why, Your Honor. The drug at
6 issue in Glaxo split in two crystalline forms,
7 those were form one and form two. The patent
8 claimed form two as defined by a very specific
9 set of 29 infrared peaks. The ANDA applicant was
10 seeking to market the other form of the drug,
11 form one, and that drug had 90 percent purity.

12 The ANDA specification revealed the
13 presence of an impurity and that impurity had one
14 of the 29 peaks required by the claim in form
15 two, but the ANDA specification said nothing
16 about whether or not that impurity would have any
17 of the other 28 peaks required by the claim for
18 there to be form two present. And that's why the
19 ANDA specification did not resolve the question
20 of infringement in the first instance, and why
21 reference to the actual products was necessary.
22 And that's not what we have here.

23 Here as in Sunovion we have a simple
24 matter of comparing the numeric ranges in the

1 '031 patent with Par's ANDA specification. And
2 Par's ANDA specification alone resolves the
3 question of infringement in the first instance.
4 It describes

5 MS. JACOBSEN: It describes a
6 product that contains acetaldehyde in the claimed
7 range. And Your Honor, that should be the end of
8 the infringement inquiry for this claim element.

9 So turning then to the first
10 question: Is acetaldehyde an antioxidant? Your
11 Honor has twice construed the term antioxidant to
12 require the presence of an agent that reduces
13 oxidative degradation.

14 And plaintiffs contend that
15 acetaldehyde is just that, an agent that reduces
16 oxidative degradation. And before I outline
17 plaintiff's proofs, I want to first acknowledge a
18 few things.

19 Acetaldehyde is not listed as an
20 antioxidant in the '031 patent. It's not listed
21 as an antioxidant in the Handbook of
22 Pharmaceuticals, and it's also not listed in the
23 FDA's inactive ingredient list.

24 And Your Honor will hear Par call

1 acetaldehyde things like an impurity and a
2 residual solvent. You'll also hear about efforts
3 that Par has taken to try to develop a product
4 without an antioxidant.

5 And, finally, Your Honor will hear
6 about batches of Par's ANDA products that contain
7 no detectable acetaldehyde.

8 But, at the end of the day, as Dr.
9 Davies will testify, there are two facts that, as
10 a matter of basic chemistry, cannot be credibly
11 disputed.

12 The first is that acetaldehyde is a
13 known reducing agent. And the second is that
14 reducing agents can act as antioxidants. And Dr.
15 Davies will go over the definition of a reducing
16 agent.

17 But, in a nutshell, reducing agents
18 are agents that are capable of undergoing
19 sacrificial oxidation. They are more readily
20 oxidized than other compounds in the system. And
21 that means that they are sacrificially oxidized
22 and can protect other compounds in the system
23 from oxidation. And that's how they reduce
24 oxidative degradation of other compounds.

1 And there's no dispute that the '031
2 patent, the exemplary antioxidant in the '031
3 patent includes antioxidants that are known to
4 function as reducing agents. And those are the
5 two highlighted here, ascorbyl palmitate and
6 ascorbic acid.

7 So we know, as a matter of basic
8 chemistry, that acetaldehyde is capable of
9 functioning as an antioxidant. The question Dr.
10 Davies will address is: How do we confirm
11 whether it is, in fact, an antioxidant?

12 And Dr. Davies' answer will be
13 simple: You test it. And that's exactly what
14 Dr. Davies did.

15 He ran a controlled head-to-head
16 stress test in the presence and absence of
17 acetaldehyde. And he demonstrated that
18 acetaldehyde causes a statistically significant
19 reduction in the oxidative degradation of
20 Rivastigmine.

21 And before I outline Dr. Davies'
22 testing in more detail, let's go over a few words
23 of terminology. The first is stress tests.

24 As Dr. Davies will explain, stress

tests are a type of test that are designed to speed up the degradation of a drug, so that the degradation can be studied in a relatively short period of time.

5 Stress tests are standard in the
6 pharmaceutical industry. And, indeed, Par's
7 manufacturing partner, 3M, conducted a stress
8 test during development of Par's ANDA products.

9 Dr. Davies will show Your Honor that
10 the '031 patent confirms that stress tests can be
11 used to test whether an agent reduces oxidative
12 degradation.

Now, Dr. Davies will explain that in designing his test, the first step was to create an oxidizing environment. And that's because without an oxidizing environment that results in appreciable degradation of Rivastigmine, it's not possible to test whether the agent in question reduces that oxidative degradation.

1 And once Dr. Davies had determined
2 experimentally the proper conditions, he ran the
3 head-to-head stress test. And that's outlined on
4 this slide.

5 So, first, Dr. Davies adds
6 Rivastigmine and an oxidizing agent to a
7 solution. That's the oxidizing environment.

8 An then he splits that solution into
9 two equal parts. And he added acetaldehyde to
10 only one of them. And that meant that he had two
11 identical solutions with only one difference
12 between them, that being the presence of
13 acetaldehyde in one of them.

14 And then Dr. Davies heated up the
15 samples to speed up the degradation and he
16 studied the degradation oxidative degradation of
17 Rivastigmine over time. And he showed that
18 acetaldehyde causes statistically significant
19 reduction in oxidative degradation of
20 Rivastigmine. The result, consistent with the
21 literature, calling acetaldehyde a reducing agent
22 and recognizing that reducing agents can act as
23 antioxidants.

24 Now, Your Honor will hear Par

1 criticize the type of test that Dr. Davies
2 conducted, the way that he conducted his test and
3 complain that he didn't conduct additional tests.
4 None of those criticisms will stand close to
5 Rivastigmine.

6 As Dr. Davies will show, Your Honor,
7 literature demonstrating that stress tests are
8 standard in the pharmaceutical industry, and he
9 will show you literature demonstrating that the
10 conditions he used for his test are within the
11 range of conditions that are commonly used,
12 including by 3M.

13 Now, of course, Dr. Davies had to
14 tailor his stress test to the exact drug and
15 antioxidant in issue in this case, but that's
16 standard in the pharmaceutical industry. Because
17 every drug is different, and not all drugs
18 undergo the same degradation in the same
19 conditions.

20 So Dr. Davies will explain to Your
21 Honor why he selected each of the conditions he
22 did for his stress test and how he determined
23 that those were the proper conditions for his
24 test.

1 Dr. Davies will also explain that
2 the type of head-to-head experiment that he did
3 is really the purist form of scientific
4 experiment. And that's because it tests only one
5 variable and nothing else.

6 And that allows Dr. Davies and
7 scientists to be certain that the observed
8 difference is due to that one variable. So his,
9 with only one difference being acetaldehyde, that
10 allowed Dr. Davies to be certain that the
11 reduction in oxidative degradation that he
12 observed was due to acetaldehyde and nothing
13 else. There's no scientific explanation, other
14 scientific explanation for it.

15 Now, of course, Par's experts could
16 have easily repeated Dr. Davies' stress test.
17 It's a standard experiment and it requires no
18 specialized equipment.

19 And Par's experts could have run any
20 one of these other tests that they say are
21 necessary, but Par's experts ran no experiments.

22 So, finally, Your Honor, Par will
23 point to the long term and accelerated stability
24 testing on batches of the ANDA products with

1 acetaldehyde and with no detectable acetaldehyde
2 and say that there's no reduction in oxidative
3 degradation in the presence of acetaldehyde.

4 But, importantly, those tests are
5 not head-to-head studies where there was only one
6 variable, the presence of acetaldehyde.

7 So it's impossible to draw any
8 conclusions about whether acetaldehyde is an
9 antioxidant from Par's stability data for at
10 least two reasons.

11 The first is Dr. Davies will explain
12 that each of the batches of Par's ANDA products
13 was made with different lots of ingredients. And
14 that gives rise to batch-to-batch variation, and
15 it means that there are many variables that could
16 have impacted the stability data.

17 And the second reason is that Par
18 only tested one patch at each time point he
19 studied the amount of oxidative degradation and
20 studied the amount of oxidative degradation in
21 one patch at each time. And as Dr. Davies will
22 explain because of the patch to patch variation
23 we just don't know to what extent the one patch
24 that Par tested is representative of the whole

1 batch which contains tens of thousands of
2 patches.

3 It could be that the patch that Par
4 tested had the lowest amount of degradation or it
5 could have had the highest amount of degradation
6 or it could have been somewhere in the middle, we
7 just don't know.

8 So that brings us back to
9 Dr. Davies' test, which is the only test that
10 will be in this case and was designed to and was
11 capable of assessing whether acetaldehyde is an
12 antioxidant and that test demonstrated that
13 acetaldehyde consistent with the literature
14 produces the oxidative degradation and is now an
15 antioxidant.

16 Just a few words then on validity.

17 Par alleges that if acetaldehyde is an
18 antioxidant and the Claim 7 of the '031 patent is
19 invalid for failing to meet the written
20 description enablement and definiteness
21 requirement of Section 112. Your Honor, the
22 plaintiff submits that Par will not be able to
23 meet its burden of proving invalidity by clear
24 and convincing evidence.

1 Now, as plaintiffs understand it,
2 Par's case appears to be that Claim 7 is limited
3 to the antioxidants specifically named in the
4 '031 patent. And if it includes any other
5 antioxidants, then it fails under 112.

6 So first, Par says that if a claim
7 term antioxidants includes antioxidants not named
8 in the specification, the term is indefinite.
9 But for a claim term to be indefinite, it has to
10 be incapable of definition. And plaintiffs, Par
11 and the Court have all provided a definition for
12 the term antioxidants. And there is no evidence
13 that whether or not a compound meets that
14 definition depends on specific tests used to
15 determine it.

16 In fact, in this case, the only test
17 that will address whether or not acetaldehyde is
18 an antioxidant will be Dr. Davies' stress test
19 and that confirmed that it is.

20 So second, Par says that there is no
21 written description for Claim 7 beyond those
22 antioxidants specifically named in the '031
23 patent. But Your Honor will hear from
24 Dr. Klibanov that the '031 patent provides a

1 written description of inventors' discovery that
2 is susceptible to antioxidants and a written
3 description of a rivastigmine transdermal device
4 containing antioxidants as recited in Claim 7.

5 And Dr. Klibanov will testify that
6 there is nothing in the '031 patent from a
7 scientific standpoint that will cause a person of
8 ordinary skill in the art to limit antioxidants
9 to those specifically named in the '031 patent.

10 Dr. Klibanov will explain that a
11 person of ordinary skill in the art in January of
12 1998 would have known that there are many
13 different antioxidants, and the person of
14 ordinary skill in the art would have recognized
15 that the '031 patent does not try to list them
16 all. And instead, it provides examples of the
17 different types of antioxidants. And those
18 include some that function as free radical
19 scavengers such as BHD and some that function as
20 reducing agents such as ascorbic acid and
21 ascorbic compound. The '031 patent also
22 discloses that antioxidants can be experimentally
23 determined to reduce oxidative degradation by
24 stress stability test and as I outlined a moment

1 ago, Dr. Davies will explain that that's exactly
2 what he did, he confirmed using a stress test
3 that acetaldehyde is an antioxidant.

4 Now, while Par's experts may now try
5 to argue that the invention is limited to the
6 antioxidants specifically named in the '031
7 patent, the weakness of Par's case is revealed by
8 the fact that it never made that argument during
9 claim construction.

10 Finally, Par argues that
11 antioxidants beyond those named in the
12 specification are not inadequate.

13 And Dr. Klibanoff will explain that
14 Claim 7 is fully enabled because whether or not a
15 compound is an agent that reduces oxidative
16 degradation can be determined by reference to the
17 '031 patent itself and the scientific literature
18 or testing with and without an antioxidant to
19 determine whether or not it reduces oxidative
20 degradation. The fact that some testing may be
21 necessary does not mean that the patent is not
22 enabled.

23 As a matter of law, the patent need
24 only set forth one way to make and use the

1 invention. And there is no dispute that the '031
2 patent describes one test that can be used to
3 test whether a compound reduces oxidative
4 degradation and those are the stress stability
5 test.

6 And so in conclusion, Your Honor, we
7 specific fully submit that Par will not present
8 clear and convincing evidence that this
9 presumptively valid claim is invalid. And we
10 respectfully submit that we will present evidence
11 that it is more likely than not the Par infringes
12 Claim 7 of the '031 patent.

13 Thank you.

14 THE COURT: Thank you, Ms. Jacobsen.

15 Mr. Brown.

16 MR. BROWN: Good morning, Your
17 Honor.

18 THE COURT: Good morning.

19 MR. BROWN: So Par's case here is
20 pretty simple. Par's ANDA product does not
21 contain about .01 percent to about .5 percent of
22 antioxidants as required by Claim 1.

23 Could I have Claim 1 up here with
24 this element highlighted.

1 Now, Par's ANDA product, the
2 transdermal patch, was developed through a
3 partnership with 3M Corporation. And actually
4 could I get a slide. 3M is famous for its
5 expertise in adhesives. They make many, many,
6 both commercial and industrial adhesives.
7 They're one of the top companies in this field,
8 and besides these commercial products they have a
9 very, very strong expertise in adhesives for
10 medical purposes including transdermal patches.

11 And the adhesive is the major
12 ingredient besides rivastigmine in Par's product.
13 I think you recall, you'll see the side-by-side
14 comparison with plaintiff's patch they have a
15 whole bunch of ingredients in there that was
16 necessitated because they couldn't have the same
17 adhesives that delivers the drugs, it sticks to
18 the skin and it contains the drug and it controls
19 all the necessary processes. An innovated
20 technology, and they succeeded in developing a
21 product that did not use an antioxidant.

22 You're going to hear testimony from
23 Jim DiZio who is an inventor of the washing
24 procedure that's used for purifying 3M adhesive

1 and he's the first named inventor on the patent
2 application in the process.

3 The Court may recall in the August
4 Watson trial Dr. Klibanov testified that he used
5 the 3M patent application that Jim Dizio is the
6 inventor on as evidence that the Watson product
7 infringed. And Dr. Klibanov specifically
8 testified about the effect that the 3M washing
9 process had on stability.

10 And so this process reliably and
11 demonstrably results in a product that is
12 essentially free of all impurities. It gets rid
13 of all of the things that are used in the process
14 of making a polymer that are reactive and can
15 cause damage to the product. And it gets rid of
16 the vast majority of the acetaldehyde and for
17 both, for all of the impurities including
18 acetaldehyde, it seems very, very small amounts
19 in all of the processes that have been made
20 following the ANDA process.

21 And I want to put up two excerpts
22 from the ANDA where Par's ANDA clearly stated to
23 the FDA that they do not use antioxidants. Here
24 is the side-by-side comparison with the

1 plaintiff's commercial patch and the middle one
2 is the Par product, the transdermal system. And
3 you can see there is the adhesive, there is
4 something called a pacifier which is isopropyl
5 and there are the components that sticks to the
6 edges of the patch that make it a patch. And
7 they don't use the rivastigmine modifier, they
8 don't have antioxidant and they don't use an
9 adhesive because they're polymer drug adhesive,
10 they don't have separate drug loading and they
11 don't have the other modifier, so the Par 3M
12 product is a much simpler patch, it doesn't
13 create the problems the plaintiff's patch does
14 and it doesn't use an antioxidant. In fact,
15 within the ANDA they say the primary pathway
16 pursued by 3M in the development was formulate
17 without an antioxidant.

18 So plaintiff's infringement theory
19 they came up with long into this case was that,
20 that acetaldehyde and antioxidant that's measured
21 in some of the batches of Par's product, sorry,
22 the acetaldehyde, an impurity is measured in some
23 of the batches of Par's product is an
24 antioxidant.

1 So Par and 3M have extensively
2 tested the stability of their products following
3 the well-known validated and standardized FDA
4 stability testing protocols. This testing
5 corresponds to one of the two testing methods
6 identified in the '031 patent. I would like to
7 pull up the column here, this is at column four,
8 lines 20 to 30. Plaintiff's counsel in opening
9 argument says the patent describes one way to
10 test for I believe it was for antioxidant
11 behavior. This column, she pointed to this, the
12 general description of stress stability test.
13 This column provides the only parameters for
14 stress stability tests that are described in the
15 patent.

16 MR. BROWN: And, first of all, they
17 are all performed on pharmaceutical compositions.
18 They're not performed as Dr. Davies did his test
19 in a test tube under different conditions.

20 Second, they define the time period
21 and temperature. So, the first one they describe
22 is a two-month stress test at 60 degrees C. And
23 the last one they describe as a three-month
24 stress test at 40 degrees C at 75 percent room

1 humidity.

2 And the second one of these tests
3 corresponds to a well-known accelerated stability
4 protocol that all pharmaceutical companies use.

5 It's one of the FDA mandated ones.

6 And so -- and Par has followed this
7 test faithfully or actually 3M followed the test
8 faithfully. And I want to point out that the
9 plaintiffs are going to be arguing, Well, you
10 should ignore this and you should listen to Dr.
11 Davies' test, and that Davies' test is actually
12 the purist science.

13 But we did not. There's no dispute
14 we didn't come up with these test parameters for
15 this litigation. These test parameters were set
16 beforehand, set by the FDA. And these are
17 generally accepted and reliable in the industry
18 and I'd like to have a look at Par's data for a
19 second to show.

20 So this is -- this slide is the 25
21 degree C, 60 percent room humidity. That is
22 what's generally to be considered ambient
23 conditions. This is where the patch sits in the
24 drug store.

1 And Par and 3M have produced tests
2 over the entire course of the shelf life of their
3 product. And the first two batches I've
4 highlighted up there are batches with no
5 detectable acetaldehyde, and then we have about
6 six other batches that have detectable
7 acetaldehyde.

8 And there's one batch that we gray
9 out for which the room temperature wasn't
10 measured. So, as you can see, after 24 months at
11 room temperature with no acetaldehyde, there's no
12 degradation.

13 Less than 0.01, when you see the
14 less than sign, what that means is that that's
15 below the measurement level of the device. And
16 so they couldn't measure any impurities after 24
17 months of the product.

18 And as you go down, as you descend
19 through the different levels of acetaldehyde that
20 was measured in the rollstock for the product,
21 you can see in three of these examples, you have
22 some oxidative degradation in the -- so there's a
23 batch 11280 has .3 and .2.

24 That's a very low level of

1 impurities, but they're forming and there's
2 acetaldehyde. So it's not stopping that from
3 happening.

4 Then, at the next batch, you have a
5 .1 instead of a less than .1. That means it was
6 detected. At one and two batches down, you have
7 another .1.

8 So at room temperature, acetaldehyde
9 is not an agent that reduces oxidative
10 degradation. But let's look at the exact test
11 that's described in the patent. This is the next
12 slide.

13 This is the 40 degree C, 75 percent
14 room humidity. And so now, if you look at the
15 six-month data, one of the two batches with no
16 acetaldehyde has a tiny bit of an impurity
17 showing up under these sort of more extreme
18 conditions. And as you walk down, you can see
19 very clearly that the addition that's
20 acetaldehyde that is appearing in some of these
21 batches is doing nothing to reduce oxidative
22 degradation.

23 And so this is an objective standard
24 test. It's the test referenced in the patent.

1 And it shows what we submit very clearly that
2 acetaldehyde is not an agent that reduces
3 oxidative degradation.

4 And plaintiff's counsel noted in
5 opening argument, also, the difference between
6 when we were here last August, they were
7 asserting that the function claims that require a
8 specific proof that the purported antioxidant is
9 working in the product producing oxidative
10 degradation, they're not saying those claims
11 anymore. And I think in looking at this data, I
12 think the Court can see why.

13 So plaintiffs support their theory
14 that acetaldehyde is an antioxidant with
15 testimony by their expert, Martyn Davies. He's a
16 pharmaceutical formulator.

17 And the pharmaceutical literature
18 simply does not support the assertion that
19 acetaldehyde is an antioxidant. And I want to
20 talk a little bit about: What is acetaldehyde
21 and go through that for a few minutes. What are
22 the chemical properties?

23 Acetaldehyde is a volatile chemical.
24 If there was a dish of acetaldehyde sitting on

1 the table here, it would probably be boiling
2 because its boiling point is about 68 degrees
3 Fahrenheit.

4 It's also known to be an oxidizing
5 agent, not an antioxidant. Our expert, Dr.
6 Ganem, is going to testify that when acetaldehyde
7 is exposed to air, it forms peroxides. It also
8 does not stop the oxidation reaction.

9 The oxidation process is a chain
10 reaction that's propagated by radicals. And one
11 of the reasons oxidation is a bad reaction for
12 pharmaceuticals and otherwise is because it's a
13 propagated reaction. It grows and it becomes a
14 chain reaction that causes a lot of damage.

15 And when acetaldehyde reacts with
16 radicals and in an oxidative environment, it
17 forms more radicals. That is not what an
18 antioxidant does. And Dr. Ganem is going to tell
19 you about that.

20 So how does Dr. Davies get to his
21 opinion that acetaldehyde is an antioxidant? It
22 was summarized very well in opening.

23 The first position is that it's
24 known in the literature as a reducing agent. And

1 it's sort of this logical chain.

2 Acetaldehyde is sometimes referred
3 to in the literature as a reducing agent. Some
4 antioxidants work as reducing agents; therefore,
5 according to Dr. Davies, acetaldehyde is an
6 antioxidant.

7 We think that position doesn't have
8 much merit. First of all, being a reducing agent
9 just means that here's something that can be
10 oxidized. The term is usually used in a very,
11 very specific context, in a particular situation,
12 this compound acts as a reducing agent.

13 And the paint on your car can be
14 oxidized. That doesn't make it an antioxidant.
15 Lots and lots and lots of compounds can be
16 oxidized.

17 The vast majority of them are not
18 antioxidants. Just being a reducing agent
19 doesn't provide, we think, a good evidence that
20 something is an antioxidant.

21 Dr. Davies' second argument is based
22 on his experimentation and we think this wholly
23 fails to show that acetaldehyde is an
24 antioxidant, i.e. an agent that reduces oxidative

1 degradation.

2 The type of test that Dr. Davies
3 conducted is called a forced degradation study.

4 He basically, as the schematics showed, he
5 dissolved Rivastigmine in a solvent in a flask
6 with none of the other ingredients that would be
7 found in a pharmaceutical formulation. And he
8 purported to measure the effect of acetaldehyde.

9 But forced degradation studies are
10 not designed or used in the pharmaceutical field
11 to determine whether a compound is an
12 antioxidant. They are not standard in the
13 industry for that purpose.

14 A standard test is standardized
15 precisely so that results from one test can be
16 compared to results from another test, and you
17 can interpret those results and draw conclusions.

18 The principal purpose in a forced degradation
19 study used for in the pharmaceutical industry and
20 the purpose of the 3M test that plaintiffs are
21 pointing to is to seriously degrade the compounds
22 at very extreme conditions to make the impurities
23 that happen when the drug breaks down.

24 It's almost like a synthetic

1 process. I want to get large quantities of these
2 so that my analytical group can do all of the
3 experimental work that they need, so I can now
4 prove I can detect very minute amounts of them in
5 my final process.

6 It's also used to get very general
7 basic chemical information about the drug, but
8 plaintiffs aren't going to be able to point to a
9 single instance in the reported literature where
10 this kind of test that's been used to evaluate an
11 oxidant behavior. And it's simply not an
12 analytical test. It's not a test used to measure
13 anything.

14 It's a test used to break your
15 product down, see what happens when it's exposed
16 to extreme conditions. But that's all it's used
17 for.

18 And we believe that Dr. Davies' test
19 results and testimony are squarely contradicted
20 by the 3M testing that I went through at the
21 beginning here. And our expert, Dr. Buckton, is
22 going to talk about the validity of those.

23 And, in particular, plaintiff's
24 batch-to-batch variability argument, we don't

1 think that that holds merit, either. The purpose
2 of an antioxidant is to reduce oxidative
3 degradation. And if it doesn't do that under
4 normal conditions that are experienced, then it's
5 not an antioxidant.

6 As plaintiff's counsel mentioned, we
7 are going to be allege that Dr. Davies' testing
8 methodology has serious detection and I want to
9 take a minute to explain why, even if you
10 disregard or if you don't believe our criticism
11 of the test, why his test is not credible
12 evidence that acetaldehyde is an antioxidant.

13 This is a little example. When I
14 was growing up, my older brother used to do this
15 trick for the neighborhood kids. He would pour
16 gasoline into a dish. He would light a match and
17 he would extinguish the match into the gasoline.
18 He would take the match, throw it into the
19 gasoline.

20 The doesn't light on fire. A lot of
21 reasons why that happens.

22 But I would submit that my brother's
23 experiment did not establish that gasoline is
24 flame retardant. And this is analogous to what

1 Dr. Davies' test is.

2 It's a single experiment under
3 extreme non-standard conditions. And even if you
4 credit as being a test as being carried out
5 directly, which we seriously dispute Dr. Davies'
6 conditions are not predictive of what will happen
7 in a pharmaceutical product or under any
8 conditions, any other conditions whatsoever or
9 even in a repeat of the same test.

10 And you may recall that before the
11 August trial, we made a Daubert motion regarding
12 Dr. Davies' testing and the Court denied that
13 without prejudice. And we would submit that, in
14 addition to their relevance as far as
15 admissibility of testing, the Daubert factor is
16 quite a good framework to evaluate the weight
17 that the test should be given.

18 And using this test for this purpose
19 has never been peer-reviewed or published. It's
20 a single experiment.

21 And Dr. Davies has not established
22 the results repeatable, and he has not
23 established any known or potential rate of error
24 for this test. There are no standards

1 controlling the operation.

2 Plaintiffs will assert this is a
3 standard test. But what Dr. Davies will testify
4 to is that it's standard not to conduct a
5 standard test, that everybody does their own
6 thing in the literature, that he sites shows that
7 basically there are no standard procedures in the
8 industry and people do whatever they want because
9 they don't care about reproducibility of the
10 results.

11 Because they're not using the test
12 for purposes of making an evaluation of anything
13 other than identifying the chemical compounds
14 that result in the break up of the drug product.

15 And so the next problem we have with
16 this test, conceptually before you get into
17 details of it is he didn't validate the test, and
18 validating a test means you provide some evidence
19 that it works for its intended purpose, that it's
20 capable of showing, in this case that it would
21 separate antioxidants from things that aren't
22 antioxidants, and he hasn't done that. He didn't
23 test alpha-tocopherol, he didn't test any
24 antioxidants. He didn't see what this test does

1 when it stays with the presence of something
2 that's wildly believed to be an antioxidant.

3 So in short we believe Dr. Davies' forced degradation study is exactly the type of litigation test that shouldn't be given much weight and at the end of the day the Court is going to be balancing the test data that 3M did which is under the FDA standard and it's the test identified in the patent versus Dr. Davies' test using conditions that have never been done before for any purpose outside of this litigation.

12 On top of it all, Dr. Davies'
13 results at the very best for plaintiffs show
14 barely any difference. Nothing like the effect
15 shown in the patent. In the patent using the
16 standard accelerated stability testing, the
17 amount of degradation products are reduced by
18 approximately four fold, and our expert,
19 Dr. Michniak-Kohn is going to testify that
20 Dr. Davies' experimental results are not
21 statistically significant, Dr. Davies is going to
22 say they are. His methodology which he
23 establishes statistical significance was
24 established after the fact and that is a serious

1 no no in statistics. But we think beyond the
2 statistics when I look at the results there is
3 hardly any difference and given the other
4 problems that we have sort of with the test, we
5 think the Court shouldn't give it very much
6 weight.

7 Now, I would like to put back Claim
8 1 back up on the screen with the highlighted
9 element and I want to take a minute to, a brief
10 minute to address plaintiff's Sunovion argument
11 that the Court raised during the pretrial
12 conference. It's a legal issue. We're going to
13 address it extensively in posttrial briefing, but
14 I want to address a factor that we believe to be
15 a major distinguishing factor in that case, which
16 is Par's ANDA does not have a specification for
17 an antioxidant. In fact, our specification says
18 we're not going to have an antioxidant. And
19 Sunovion addresses the situation, I think the
20 words plaintiff's counsel used was where the ANDA
21 directly addresses the question of infringement,
22 what that means is you look at the ANDA and if
23 you can see infringement without leaving the ANDA
24 you're going to apply the Sunovion standard and

1 you don't consider other evidence.

2 But that doesn't apply here and
3 plaintiffs admitted it doesn't apply here because
4 when I sit down Dr. Davies is going to stand up
5 and say something that's not been described in
6 the patent or otherwise as *****an antioxidant
7 is an antioxidant. So this is very different.

8 In fact, if you look at the Glaxo case, the only
9 reason Sunovion distinguished Glaxo was that from
10 the 90 percent to 0 was form one and they didn't
11 put a label on what was from 90 percent to a
12 hundred percent. The facts of the case there
13 were only two forms and so they're very well,
14 that very well could be effectively a
15 specification permitting up to ten percent of
16 form two, but the ANDA specification didn't say
17 form two, you had to go outside the ANDA
18 specification to find out if that was or was not
19 in fact form two. And once you did, you had to
20 consider all the relevant evidence about what the
21 ANDA applicant would likely sell.

22 So we submit that, and we think
23 there is a lot of other reasons to distinguish
24 Sunovion in this case, but we submit that since

1 your ANDA specification does not resolve the
2 question of infringement because we say we don't
3 have an antioxidant *****and, therefore, the
4 plaintiffs, and you have to look at other
5 evidence to make that determination, we think
6 that is a significant distinguishing factor of
7 Sunovion.

8 Now another big difference is that
9 case was based on a piece of paper somebody put
10 into the Court and I believe in that case they
11 actually spike their sample with the other
12 product. I did want to point in the ANDA
13 specification identified a particular chemical,
14 it was levetiracetam, the specification and the
15 claim element identified the exact same thing.
16 And here, this is different because our ANDA
17 specifications are acetaldehyde, the claim
18 element is for an antioxidant. And that is
19 something different.

20 Another different is there are now
21 batches of Par ANDA product that have been
22 manufactured using the ANDA product for which
23 acetaldehyde measurements have been taken, two
24 batches have no detectable acetaldehyde, the

1 other six batches the acetaldehyde was measured
2 to be between eight parts per million and 30
3 parts per million.

4 And to cover our actual ANDA product
5 plaintiffs have to resort to the term in the
6 claim and they got to stretch their claim pretty
7 far if they're going to cover the actual product
8 made using the ANDA process, and when we were
9 heading to trial in August, the court in ruling
10 on our Daubert motion cited a case called
11 Cohesive Technologies that the Court believed was
12 relevant to the interpretation, so I wanted to
13 address that case for a couple of minutes.

14 So essentially in the Cohesive
15 Technologies case the Federal Circuit said when
16 you're addressing the lower end of a numerical
17 range you need to look at the function that the
18 numerical range has in the invention. And here,
19 so if we're going to look at the function of the
20 numerical portion of this element, this was added
21 during prosecution, in response to a rejection by
22 the patent office that the patentees had not
23 enabled all antioxidants at all concentrations so
24 they added the about language to the limitation.

1 And the specification here describes
2 experimental data from only one antioxidant and
3 at two concentration, .1 and .15 and those are
4 both well within the claim, so from the
5 prosecution history, the function of the range is
6 to enable a person of ordinary skill in the art
7 to stabilize a pharmaceutical composition, and if
8 we look at the specification, I would like to
9 pull up column four, line 16 to 30. Here is the
10 only place in the specification that the
11 numerical range appears and immediately following
12 it, they give two examples where the
13 pharmaceutical compositions of the invention are
14 reducing degradation in one case from 4.46, from
15 1.09 to .25 percent. While we realize that the
16 Court has construed antioxidants that it does not
17 have to function in the formulation, we submit
18 that when plaintiff's resort to the about
19 limitation to try to capture something that's not
20 within the numerical range, they're bringing back
21 functionality in the claim through the Cohesive
22 Technology, then they have to show that our
23 amount of acetaldehyde functions like the amount,
24 the claimed amounts of antioxidants.

1 And we submit that this again, same
2 stability data shows unequivocally acetaldehyde
3 doesn't do anything in our product.

4 And then on infringement, I think
5 the Court knows, discussed in the pretrial
6 conference we also have our declaratory judgement
7 claim for the '023 patent that's in the case, and
8 I want to then jump ahead and talk briefly about
9 our 112 invalidity case that the plaintiffs
10 address in their opening.

11 If the Court were to credit
12 Dr. Davies's study, that presents a different
13 problem for plaintiffs. Since those results at
14 least according to plaintiffs are different from
15 the results of 3M's FDA approved stability
16 testing using a test that is specified in the
17 patent, that means using different test methods
18 yields different results.

19 And the crux, an important
20 components of our indefiniteness test is that
21 under plaintiff's interpretation of how you show
22 infringement, there is no principal way to
23 determine what is or is not an antioxidant.
24 Competitors are entitled to know the scope of the

1 patent. And even if Dr. Davies' test is one way,
2 there are infinitely other ways and references he
3 cited and otherwise to conduct a forced
4 degradation. Even if we did ten tests that
5 showed no effect, Dr. Davies can design an
6 eleventh test with some unknown chemical in it,
7 he can come up with some new set of test
8 circumstances that he says show some minor
9 effect, he now can wave that around and say, I
10 discovered a new antioxidant, and that's not a
11 legitimate scope of a claim. The public is
12 entitled to know and to be able to determine if
13 they're inside or outside the claim, and the case
14 we cite for that and Amagen versus Herch 314
15 F.3rd 1313, the enablement defense is similar.
16 Like the patent office rejection during
17 prosecution we are asserting the full scope of
18 this claim is not enabled and particularly the
19 full scope the plaintiffs are asserting that that
20 the compound doesn't have to be established
21 according to them to be an antioxidant by any
22 established test, nor does it have to be an
23 antioxidant for anything in particular, you know,
24 according to my previous example, I think, you

1 know, the paint on your car can be oxidized, I
2 think the plaintiff's definition would encompass
3 Turtle Wax because I can put Turtle Wax on my car
4 and it can stop oxidizing. They have really not
5 been able since the scope of their claim that
6 they're asserting is not limited by reducing
7 oxidation of any particular thing under any
8 particular environment, we think they clearly
9 have not enabled a person of ordinary skill in
10 the art to use that scope of compound as an
11 antioxidant in a pharmaceutical formulation.

12 The written description defense is
13 similar, the difference between the written
14 description and the enablement defense
15 conceptually is the written description you look
16 only at what's in the specification and you use
17 ask the question whether the inventors were in
18 possession of the invention as it's claimed, and
19 here, they have described data for one
20 antioxidant, we know in fact they tested one
21 other one, and it didn't work, they have data
22 from two, one worked, one didn't work and from
23 that, they extrapolated to claim any chemical
24 compound in their words capable of reducing

1 oxidation of any other compound any other
2 circumstances in any test and we would submit
3 they don't have written description enablement or
4 definiteness support for that scope.

5 Thank you, Your Honor.

6 THE COURT: Thank you, Mr. Brown.

7 Novartis, call your first witness.

8 MS. JACOBSEN: Plaintiff's first
9 witness is Martyn Davies. And he'll be providing
10 the infringement testimony.

11 THE COURT: Thank you.

12 THE CLERK: Please state and spell
13 your full name for the record.

14 THE WITNESS: My name is Martyn,
15 M-A-R-T-Y-N, Christopher Davies, D-A-V-I-E-S.

16
17 MARTYN CHRISTOPHER DAVIES, PH.D.,
18 the deponent herein, having first
19 been duly sworn on oath, was
20 examined and testified as follows:

21 THE COURT: Could I just ask both
22 counsel to move the microphone a little closer to
23 your mouth. You're both very soft spoken and I
24 heard what you said, but it's a challenge. It

1 shouldn't be a challenge.

2 MS. JACOBSEN: Yes, Your Honor.

3 Your Honor, can we approach?

4 THE COURT: Yes.

5 MR. FINEMAN: Your Honor, quick
6 housekeeping before we start, does Your Honor
7 want to address objections as they come along or
8 would Your Honor want to wait to the end?

9 THE COURT: You should objection as
10 we come along.

11 MR. FINEMAN: Thank you.

12 DIRECT EXAMINATION

13 BY MS. JACOBSEN:

14 Q. Good morning, Dr. Davies.

15 A. Good morning.

16 Q. Can you please state your full name for
17 the record?

18 A. My name is Martyn Christopher Davies.

19 Q. And Dr. Davies, do you have a binder of
20 documents in front of you there?

21 A. I do.

22 Q. And can you turn to tab one, you'll find
23 PTX 50A. Can you please identify that document
24 for the Court?

1 A. That's my curriculum vitae.

2 MS. JACOBSEN: Your Honor,

3 plaintiffs moved to introduce into evidence PTX

4 50A.

5 MR. BROWN: No objection.

6 THE COURT: Admitted without

7 objection.

8 MS. JACOBSEN: And, Your Honor,

9 based on your comments at the pretrial

10 conference, we don't plan to go through his

11 qualifications.

12 THE COURT: I'm satisfied. Is there

13 any objection to him testifying as an expert?

14 MR. BROWN: No, Your Honor.

15 THE COURT: You may proceed.

16 MS. JACOBSEN: Thank you, Your

17 Honor.

18 BY MS. JACOBSEN:

19 Q. Dr. Davies, can you please summarize what

20 you were asked to do with respect to Par ANDA

21 products?

22 A. Yes. I was asked to see whether Par's

23 ANDA products meet the elements of Claim 7 of the

24 '031 patent. And in particular I was asked if

1 the acetaldehyde is an antioxidant. Is it an
2 agent that reduces oxidative degradation. And
3 also I was asked if acetaldehyde was present in
4 the amounts that are in the claims of Claim 7.

5 Q. Can you summarize your analysis with
6 respect to the first issue, whether acetaldehyde
7 is an antioxidant?

8 A. Yes. It was a matter of, if one looks
9 simply first at the basic chemistry of
10 acetaldehyde, acetaldehyde is firstly known as a
11 reducing agent, and reducing agents act as
12 antioxidants. And with that basic chemistry
13 understanding, I then undertook an experiment to
14 show that acetaldehyde is an antioxidant.

15 Q. What type of experiment did you run?

16 A. I ran a controlled head to head stress
17 test where I created an oxidative environment, I
18 placed the rivastigmine within that environment in
19 the presence or absence of acetaldehyde. So I
20 created an experiment which in many ways is the
21 simplest form of experiment where there is only
22 one variable. That one variable being the
23 presence or absence of acetaldehyde

24 A. And I monitored the degradation that

1 occurred in the assay of the drug in the presence
2 or absence of acetaldehyde.

3 Q. And what did that experiment show?

4 A. That experiment showed that acetaldehyde
5 is an agent which reduces oxidative degradation.
6 And it also showed that acetaldehyde is an
7 antioxidant.

8 Q. Can you summarize your analysis with
9 respect to the second issue, whether Par's ANDA
10 product contains about 0.01 to about 0.5 weight
11 percent of acetaldehyde?

12 A. Yes. If you look at Par's specification,
13 the specification cites for acetaldehyde that it
14 can be present in up to a thousand parts per
15 million. That is 0.1 percent which falls directly
16 within the range of the claim.

17 Q. Is that the specification for all three of
18 Par's ANDA products?

19 A. That's correct.

20 Q. What was the basis for Par's ANDA
21 specification for acetaldehyde?

22 A. Par ran its own evaluation of the toxicity
23 of acetaldehyde and they also measured the levels
24 in their prototype batches at -- they set the

1 specification to up to a thousand parts per
2 million.

3 Q. Thank you, Dr. Davies.

4 Let's discuss briefly Par's ANDA
5 products and their structure. And can you please
6 describe Par's ANDA products for the Court?

7 A. Yes. A very simple diagram which just
8 illustrates the point.

9 Par has three products. It has an
10 -- excuse my tremor -- 4.6, a 9.5 and a 13.3
11 milligram per 24-hour patches. These all contain
12 the same ingredients.

13 They have a backing layer. They
14 have a release liner. And they have a single
15 drug-in-adhesive layer. And that single
16 drug-in-adhesive layer contains Rivastigmine. It
17 contains the isopropyl myristate, which is the
18 tackifier. And it contains the acrylate
19 copolymer adhesive, which contains acetaldehyde.

20 Q. And can you please turn to Tab 2 of your
21 witness book and there you'll find PTX 344. Can
22 you identify that document for the Court?

23 A. This is a portion of Par's ANDA which
24 highlights the structure and also the composition

1 of the three different dosage strengths of Par's
2 ANDA products.

3 MS. JACOBSEN: And, Your Honor,
4 plaintiff moves to introduce into evidence PTX
5 344.

6 MR. BROWN: No objection.

7 THE COURT: Admitted without
8 objection.

9 MS. JACOBSEN: And for the record
10 Dr. Davies referred to PTX 344 at Page 231.

11 BY MS. JACOBSEN:

12 Q. Dr. Davies, can you describe how you
13 determined whether Par's ANDA products meet the
14 elements of Claim 7?

15 A. Yes. I broke the claim down into the key
16 elements and then I compared those elements with
17 Par's ANDA product to come to my opinion.

18 Q. And can you walk us through those
19 elements, please, Dr. Davies?

20 A. Yes, certainly.

21 It is a transdermal device -- sorry.
22 A transdermal device, which has pharmaceutical
23 composition comprising of therapeutically
24 effective amounts of -- this is Rivastigmine.

1 Has an antioxidant with about 0.01 to about 0.5
2 percent by weight. A diluent or carrier and
3 wherein the pharmaceutical composition is
4 supported by a substrate.

5 Q. Dr. Davies, can you please turn to Tab 3
6 of your witness binder? And there you'll find
7 JTX 1.

8 Can you please identify that
9 document?

10 A. That's the '031 patent from which Claim 7
11 shown here is drawn.

12 MS. JACOBSEN: And, Your Honor,
13 plaintiff moves to introduce into evidence JTX 1,
14 the '031 patent.

15 MR. BROWN: No objection.

16 THE COURT: Admitted without
17 objection.

18 BY MS. JACOBSEN:

19 Q. Dr. Davies, do you have an understanding
20 as to which elements are actually in dispute in
21 this case?

22 A. Yes. It's whether or not there's an
23 antioxidant present in Par's products and whether
24 it's present in about 0.01 to about 0.5 percent

1 by weight in the three.

2 Q. And Dr. Davies, I'd like to start with the
3 first issue, whether Par's ANDA products contain
4 an antioxidant. Are you aware of how this Court
5 has construed the term antioxidant?

6 A. Yes. It says that the antioxidant
7 requires the presence of an agent that reduces
8 oxidative degradation as shown on this slide.

9 MS. JACOBSEN: And for the record,
10 Dr. Davies is referring to the '031 patent in JTX
11 1 and the Court's claim construction DI-250.

12 BY MS. JACOBSEN:

13 Q. Do Par's ANDA products contain an
14 antioxidant under the Court's claim construction?

15 A. Yes, I believe they do. They contain
16 acetaldehyde.

17 Acetaldehyde, which I will show is
18 known as a reducing agent. Reducing agents can be
19 antioxidants. And my test shows that it is an
20 antioxidant.

21 Q. And how do you know that Par's ANDA
22 products contain acetaldehyde?

23 A. Well, the specification states quite
24 clearly that it contains acetaldehyde. Contains

1 acetaldehyde up to the order of a thousand parts
2 per million.

3 3M, who is Par's manufacturer, also
4 detected the acetaldehyde and makes the adhesive.

5 Q. Dr. Davies, what is an ANDA specification?

6 A. An ANDA specification is a document
7 submitted to the FDA where a company is seeking
8 regulative approval to market a particular
9 product. The ANDA specification is a blueprint
10 of all the information the FDA requires for it to
11 be able to assess the products and its
12 suitability for regulatory approval.

That includes information related to
the manufacture, the properties of the compounds
present, and it also includes information
pertinently related to the specification.

17 And the company, when it submits its
18 ANDA with those specifications, if that
19 particular ANDA is approved and the product
20 approved for marketing the company can actually
21 manufacture their product to meet those
22 specifications.

23 Q. Dr. Davies, can you please turn to Tabs 4,
24 5 and 6 of your witness book? And there you'll

1 find documents marked PTX 348, 349 and 350.

2 And can you please identify those
3 documents?

4 A. These are the specification for the
5 finished product for the 4.6, the 9.5 and the
6 13.3 milligram, the three different dosage
7 strengths for Par's product respectively.

8 Q. Can you identify where in Par's ANDA
9 specification the limit for acetaldehyde is set?

10 A. Yes. This slide shows -- this is taken
11 from a portion of a finished product
12 specification. It shows the one for the 13.3
13 milligram per 24 hours.

14 And you see that it has here NMT
15 1000 parts per million acetaldehyde. The NMT
16 means not more than.

17 And you see the same specification
18 in all three dosage strengths.

19 Q. What does the parenthetical
20 monomer-related mean?

21 A. That means that the acetaldehyde is in the
22 adhesive -- it's present within the adhesive.
23 The adhesive that Par mixes with its drug and to
24 create its drug-in-adhesive layer.

1 MS. JACOBSEN: Plaintiffs move to
2 introduce PTX 348, 349, and 350 into evidence.

3 MR. BROWN: No objection.

4 THE COURT: Admitted without
5 objection.

6 MS. JACOBSEN: And for the record,
7 the pages referred to by Dr. Davies are PTX 348
8 at Page 780, PTX 349 at Page 788, and PTX 350 at
9 Page 796.

10 BY MS. JACOBSEN:

11 Q. Dr. Davies, how did you analyze whether
12 acetaldehyde is an antioxidant?

13 A. As I explained, I -- firstly, I looked at
14 the chemistry. I looked at the chemistry of
15 acetaldehyde. It's a well-known reducing agent.

16 And reducing agents can act as
17 antioxidants. And so then I took tests -- a test
18 that demonstrated that acetaldehyde is an agent
19 which reduces oxidative degradation.

20 Q. Dr. Davies, can you please explain what
21 reducing agents are?

22 A. It's -- yes. Reducing agents are agents
23 that will undergo sacrificial oxidation in a
24 mixture such that they help to protect other

1 agents that -- other compounds such as drugs that
2 may be present. So they're more susceptible, in
3 that sense, to oxidation.

4 So reducing agents can act -- will
5 undergo sacrificial oxidation reducing the level
6 of the oxidative environment; and therefore,
7 helping to protect the drug.

8 Q. And after you considered the basic
9 chemistry, what was the next step in your
10 analysis?

11 A. The next step in my analysis was to create
12 an experiment where I undertook a stress test, a
13 controlled stress test which was a head-to-head
14 stress test where I created an oxidative
15 environment where an oxidative environment which
16 would degrade the drug. And then I compared that
17 oxidation, what would happen if I had a sample
18 with and without acetaldehyde.

19 Q. And what do you mean with a controlled
20 head-to-head test?

21 MR. BROWN: Your Honor, in your
22 order denying our Daubert motion, you mentioned
23 that at trial to preserve that, we should renew
24 our Daubert request. So I'm issuing a Daubert

1 objection to Dr. Davies' testimony and I would
2 request that the Court grant me a continuing
3 objection, so I don't need to do this further
4 during the trial.

5 THE COURT: Well, I'll grant you a
6 continuing objection to at least this particular
7 testing --

8 MR. BROWN: Correct.

9 THE COURT: -- which I think, as I
10 understand, is what you're objecting to. And
11 basically I think, based on the pretrial ruling,
12 the pretrial ruling, I'll expect Dr. Davies will
13 explain what it's in the test. And then probably
14 your expert will explain why it's not.

15 And I'll figure that out later on.

16 MR. BROWN: Thank you, Your Honor.

17 THE COURT: All right. You may
18 proceed, Ms. Jacobsen.

19 MS. JACOBSEN: Thank you.

20 BY MS. JACOBSEN:

21 Q. So, Dr. Davies, you used the term
22 controlled head-to-head test. Can you please
23 explain what you meant by that?

24 A. Yes. When I'm saying it's a head-to-head

1 test, what I'm saying there is that this is a
2 test where there's only one variable in play. In
3 this case, it's the presence or absence of
4 acetaldehyde. Everything else remains the same.

5 So if there -- if I show between
6 these two sets of samples, one of which has no
7 acetaldehyde, one of which has acetaldehyde
8 present, the only difference between these two
9 samples is the absence or presence of
10 acetaldehyde.

11 So if there's any difference between
12 these two samples related to the oxidative
13 degradation of the drug, it could be attributable
14 directly to the presence of just that one
15 variable, i.e. the absence or presence of
16 acetaldehyde.

17 Q. And what were the results of your stress
18 test?

19 A. The results of my stress test showed that
20 acetaldehyde reduced the oxidative degradation.
21 It was also -- my stress test showed that
22 acetaldehyde is an antioxidant.

23 Q. Did you conduct any statistical analysis
24 on your results?

1 A. Yes, I did. I conducted statistical
2 analysis to show that the difference between the
3 two samples, the two sets of samples, the only
4 variable in play with or without acetaldehyde was
5 statistically significant. I showed that it was
6 statistically significant.

7 Q. And did you draw any conclusions from your
8 experiment?

9 A. I did. I drew the conclusion that, based
10 on my experiment, that acetaldehyde is an agent
11 which reduces oxidative degradation. That backed
12 up what I knew from the literature.

13 And what I knew about acetaldehyde
14 is it is a known reducing agent, and reducing
15 agents can be antioxidants. And my data clearly
16 shows in this very simple and very straight
17 forward, very pure, in a sense, experiment, that
18 it is. Acetaldehyde is an antioxidant.

19 Q. Thank you, Dr. Davies.

20 Does the '031 patent list
21 acetaldehyde as an antioxidant?

22 A. No, it does not. It lists exemplary
23 examples. Sorry.

24 I show this slide here, which lists

1 them, a number of examples in, I believe, it's
2 Column 4.

3 Q. Did the fact that acetaldehyde is not
4 listed in the '031 patent influence your
5 infringement analysis in any way?

6 A. No, it does not. It's not -- this list is
7 not limited to be -- it's not -- pardon. It
8 doesn't limit the antioxidants that can be used
9 to this specific list.

10 The claims are quite clear that it
11 -- they relate to antioxidants. They're not
12 limited to specific antioxidants in Claim 1 or
13 Claim 7.

14 Q. Does the '031 patent describe any reducing
15 agents as antioxidants?

16 A. Yes, it does. It describes ascorbic acid
17 and ascorbyl palmitate, both of which are both
18 reducing agents.

19 MS. JACOBSEN: And for the record,
20 the passage from the '031 patent, JTX 1 that Dr.
21 Davies is referring to is at Column 4, Lines 10
22 to 19.

23 BY MS. JACOBSEN:

24 Q. Dr. Davies, are you aware of any

1 literature calling acetaldehyde a reducing agent?

2 A. This is at slide -- a page from Van

3 Nostrand's Concise Encyclopedia of Science.

4 There's a monograph here for acetaldehyde.

5 And it says the compound also is used

6 as a reducing agent.

7 MS. JACOBSEN: And, Your Honor,

8 Plaintiffs move to introduce into evidence JTX 61.

9 MR. BROWN: No objection.

10 THE COURT: Admitted without

11 objection.

12 MS. JACOBSEN: And for the record,

13 Dr. Davies referred to JTX 61 at Page 5.

14 BY MS. JACOBSEN:

15 Q. Is there any other evidence that

16 acetaldehyde is capable of being oxidized itself

17 to protect other compounds from oxidation?

18 A. Yes. This is a slide, again, from a page

19 taken from a pharmaceutical textbook called

20 Modern Pharmaceutics.

21 And there's a section here on

22 oxidation. And in the section on oxidation, it

23 talks about, in pharmaceutical dosage forms,

24 oxidation is usually mediated through reaction

1 with atmospheric oxygen and under ambient
2 conditions, a process commonly referred to as
3 autoxidation.

4 And the next paragraph, it goes on
5 to talk about many autoxidation reactions are
6 initiated by trace amounts of impurities, such as
7 metal ions or hydroperoxides.

8 Now, if you look below, there's a
9 table where it talks about some functional groups
10 subject to autoxidation. And it highlights
11 acetaldehydes here. Sorry, it highlights
12 aldehydes here.

13 And acetaldehyde is one of the
14 simplest forms of aldehyde.

15 Q. Why is this relevant to your analysis?

16 A. It's relevant to my analysis because it
17 demonstrates that -- it shows that aldehydes are,
18 such as acetaldehyde, are subject to
19 autoxidation. In other words, aldehydes act as
20 reducing agents.

21 MS. JACOBSEN: Your Honor,
22 plaintiffs move to introduce into evidence JTX
23 106.

24 MR. BROWN: No objection, Your

1 Honor.

2 THE COURT: Admitted without
3 objection.

4 MS. JACOBSEN: And for the record,
5 Dr. Davies referred to JTX 106 at Page 183.

6 BY MS. JACOBSEN:

7 Q. And Dr. Davies, is there any other
8 evidence that reducing agents can act as
9 antioxidants?

10 A. Yes. This is a slide from, again, a page
11 taken from the EMEA Note for Guidance. EMEA is
12 the European equivalent to the FDA.

13 And there's a section here on
14 antioxidants. And it shows antioxidants are used
15 to reduce the oxidation of active substances and
16 excipients in the finished product.

17 And it highlights, there are three
18 different types of antioxidants, one of which is
19 reducing agents. And it says these have a lower
20 redox potential than the drug or excipient they
21 are protecting. What that means is that the more
22 susceptible to oxidation and they'll
23 sacrificially undergo oxidation so that they're
24 able to protect the drug excipient.

1 It gives an example of ascorbic acid
2 and ascorbic acid is one of the examples that we
3 seen in the '031 patent.

4 MS. JACOBSEN: Your Honor,
5 plaintiffs move to introduce into evidence JTX
6 105.

7 MR. BROWN: No objection.

8 THE COURT: Admitted without
9 objection.

10 MS. JACOBSEN: And for the record,
11 Dr. Davies referred to JTX 105 at page one of
12 four.

13 BY MS. JACOBSEN:

14 Q. And Dr. Davies, have you seen any other
15 evidence of reducing agents can act as
16 antioxidants?

17 A. Yes. This is another section from Modern
18 Pharmaceutics, and it's a section again dealing
19 with in this case antioxidants. And talks about
20 mechanistically some antioxidants such as
21 ascorbic acid and ascorbic palmitate, those are
22 the two that I highlighted again from the
23 examples in the '031 patent, act as reducing
24 agents. They are easily oxidized, preferentially

1 undergo autoxidation, thereby consuming oxygen and
2 protecting the drug or excipient.

3 MS. JACOBSEN: For the record,

4 Dr. Davies referred to JTX 106 at page 203.

5 BY MS. JACOBSEN

6 Q. Is acetaldehyde listed in the FDA inactive
7 ingredient list?

8 A. No, it is not.

9 Q. Are you aware of acetaldehyde being used
10 in pharmaceuticals?

11 A. Yes, this is the specialty chemicals
12 sourcebook and, again, it's got a monograph for
13 acetaldehyde. And under the uses, it cites
14 synthetic flavoring agent in foods, beverages and
15 pharmaceuticals. And it also cites that it's
16 used in the manufacture of pharmaceuticals.

17 And if you look at its regulatory
18 status, its status is GRAS, which is general, the
19 term for generally regarded as safe. And as
20 given by the FDA --

21 Q. And Dr. Davies, I think you misspoke, you
22 said generally regarded as safe. Is it generally
23 recognized as safe?

24 A. I believe that's true, yes. Sorry.

1 Q. Thank you.

2 And are you aware of any products in
3 which acetaldehyde is permitted to be present?

4 A. Yes. The Par product where it's present.

5 MS. JACOBSEN: Your Honor, plaintiff
6 move to introduce into evidence JTX 63.

7 MR. BROWN: No objection.

8 THE COURT: Admitted without
9 objection.

10 MS. JACOBSEN: And for the record,
11 Dr. Davies referred to JTX 63 at page 7.

12 BY MS. JACOBSEN:

13 Q. So focusing on rivastigmine specifically,
14 can you explain what happens when rivastigmine is
15 oxidized?

16 A. Yes. This is the generally recognized by
17 Par, I don't think there is any dispute about
18 this regarding rivastigmine oxidative degradation
19 pathway. Here is the rivastigmine molecule, it
20 can undergo oxidation by oxygen or peroxides to
21 form what is called an N-oxide here. The N-oxide
22 has a very short half life, and it degrades to
23 form, the styrene molecule here. The styrene
24 molecule is referred to as ECAV by Par. That

1 molecule can undergo further oxidation by oxygen
2 or peroxides to form the ketone, and that's known
3 as impurity 4.

4 Q. Are oxidative degradation products
5 different if rivastigmine is oxidized by oxygen
6 or peroxide?

7 A. No, they're the same. In fact, these are
8 the two key degradation products that are seen
9 for the oxidative degradation of rivastigmine,
10 whether by oxygen or by peroxides.

11 Q. Can you explain how an agent, reducing
12 agent such as acetaldehyde can act as an
13 antioxidant?

14 A. Yes. I have shown it on this slide.
15 Reducing agents such as acetaldehyde will
16 sacrifice themselves and react with the oxygen or
17 peroxides so reducing the oxidative degradation,
18 and they will do that in this case block the
19 conversion of the rivastigmine to the, they'll
20 react with the oxygen or peroxides, they'll also
21 at this point with the conversion of the styrene
22 to ketone, acetaldehyde will sacrifice itself
23 and react with the oxygen and peroxide thereby
24 reducing the oxidative degradation.

1 Q. Dr. Davies, can you please turn to tabs 11
2 and 12 of your witness book and there you'll find
3 JTX 85 and PTX 125. Can you please identify
4 those documents?

5 A. Again, they're part of the Actavis
6 technical documents, the first, and then there is
7 also you said 12.

8 Q. Tab 12, should be PTX 125?

9 A. I'm sorry, I'm looking at the wrong
10 document. I apologize. Tab 12, yes, that's an
11 E-mail correspondence from Actavis. I'm happy to
12 talk about it, if you wish me to talk about it.

13 Q. I will.

14 MS. JACOBSEN: We'll move to
15 introduce as exhibits into evidence JTX 85 and
16 PTX 125.

17 MR. BROWN: We have an objection to
18 PTX 125 as hearsay. This is an Actavis E-mail.
19 They're not a party to the litigation, and
20 they're introducing it for I believe statements
21 that are in for the truth of the matter asserted
22 and we would object to PTX 125 on those grounds.

23 THE COURT: Ms. Jacobsen.

24 MS. JACOBSEN: This is an E-mail

1 from Actavis. Actavis used to own Par's ANDA.
2 It's an admission against interest by Par's
3 predecessor so it's admissible under 801(d)2(b).

4 THE COURT: All right. Do you agree
5 that Actavis was Par's predecessor?

6 MR. BROWN: Actavis was the previous
7 owner of the ANDA, that is correct.

8 THE COURT: All right. I'm going to
9 tentatively admit it. If it turns out that you
10 want to present in posttrial briefing that this
11 was a mistake, go ahead, but I think it's
12 admissible. Go ahead.

13 MS. JACOBSEN: Thank you, Your
14 Honor.

15 For the record, Dr. Davies referred
16 to JTX 85 at page 2403 and PTX 125 at page 33980.

17 BY MS. JACOBSEN:

18 Q. Dr. Davies, I would like to transition now
19 to the experiment that you conducted. Just so
20 the record is clear, Dr. Davies, can you go to
21 Tab 12 again in your witness book, and that's
22 where PTX 125 is?

23 A. Yes.

24 Q. And can you turn to page 980, page ending

1 in 980, and can you explain what this document
2 relates to?

3 A. Yes. This is called the E-mail from Dale
4 Martin at Actavis, and in the third paragraph
5 down, he's talking about an impurity is an
6 oxidation impurity and its formation is promoted
7 by the presence of oxygen, especially peroxides
8 and like. So he's recognizing that oxygen and
9 peroxides are responsible for the oxidative
10 degradation of rivastigmine.

11 Q. Thank you, Dr. Davies.

12 Now I would like to transition to
13 the experiment that you conducted.

14 MS. JACOBSEN: Sorry, Your Honor.
15 One other matter. On JTX 85, I understand it's
16 not clear whether that was admitted.

17 THE COURT: I'm sorry. It was
18 admitted without objection, or it is now admitted
19 without objection.

20 MS. JACOBSEN: Thank you, Your
21 Honor.

22 BY MS. JACOBSEN:

23 Q. Now, I would like to transition to your
24 testing. Can you briefly explain how you

1 approached the design of your experiment?

2 A. First thing I wanted to do was create
3 conditions where -- such that I created an
4 oxidizing environment such that I could monitor
5 the oxidative degradation of rivastigmine.

6 Q. Why did you want to create an oxidizing
7 environment?

8 A. Well, the reason I wanted to do it because
9 I wanted to be able to create an environment
10 where I am replicating the oxidative degradation
11 pathway of rivastigmine so I'm able to show the
12 presence of these two key degradation products,
13 and I wanted to do that at a sufficient level
14 such that I could then undertake an experiment,
15 undertake an experiment where I compared two sets
16 of solutions, one with and without the presence of
17 acetaldehyde to see whether or not acetaldehyde
18 had any influence on the formation of those two
19 degradation products of the oxidative degradation
20 pathway.

21 Q. What did you do once you established the
22 conditions for an oxidizing environment?

23 A. Once I established that, I then set up the
24 experiment in a way that I created an experiment

1 where I created two sets of samples, one of which
2 had no acetaldehyde present, one set, another set
3 which had acetaldehyde present. So I was
4 creating my head to head stress test.

5 The one without acetaldehyde acted as
6 the control for the samples with acetaldehyde.
7 There is only one variable here, the presence or
8 absence of acetaldehyde, therefore, any
9 differences in the levels of these two key
10 components could be attributable to the presence
11 or absence of acetaldehyde.

12 Q. Dr. Davies, you used the term stress test.
13 What is a stress test?

14 A. A stress test is a test used widely within
15 the pharmaceutical industry. And they're used to
16 accelerate the degradation of a drug or excipient
17 so that you can monitor that degradation over a
18 short period of time.

19 Q. Can stress tests be used to study
20 different degradation pathways?

21 A. Yes, it can. And it is used, and it's
22 widely used for that effect. So, for example,
23 one can study the influence of light, you could
24 study the influence of acid or basic conditions.

1 You could study the influence of oxidation.

2 There are a number of things that one could do.

3 Q. Can stress tests be used to determine
4 whether something is an antioxidant?

5 A. Yes, it can. Because having established
6 with the stress test that you are able to -- a
7 particular pathway as we have shown here, as I
8 will show -- you can in the kind of experiment
9 that I have undertaken, a controlled head to head
10 study, you can show whether or not a molecule is
11 an antioxidant by doing the controlled head to
12 head study by having a control and then having a
13 sample with say in this case acetaldehyde in that
14 stress test. Any differences in the rate of the
15 degradation could be attributable to the one key
16 variable that's changing, the presence or absence
17 of acetaldehyde.

18 Q. And is it necessary for all the conditions
19 to be the same to run a head to head test?

20 A. It is for this, I believe it is, because
21 in that controlled stress test you have a test
22 where there is only one variable in play, so any
23 differences between the two sets of samples could
24 be directly attributable to that one variable.

1 However, if you have multiple
2 variables occurring, the multiple differences
3 between the samples, then you can't be sure that
4 any differences that you do observe could be
5 attributable to the presence or absence in this
6 case of acetaldehyde.

7 Q. Are stress tests standard in the
8 pharmaceutical industry?

9 A. Yes, it is. This is a paper by Alsante.
10 It talks of stress testing is a critical
11 component of drug development. It says by
12 generating key stress-testing samples (i.e.,
13 partially degraded samples stressed under various
14 conditions), predictive degradation information
15 can be obtained early in the process. Stress
16 testing can help in the selection of more stable
17 drug substance salt forms and drug formulations.

18 So that can help in the selection of
19 the most appropriate drug forms to use and also
20 which excipients to use to make a stable
21 composition.

22 Q. Are there any other references discussing
23 the use of stress tests in the pharmaceutical
24 industry?

1 A. Yes. There is a reference by Aubry, it
2 talks about the development of stability
3 indicating methods. And here, it says forced
4 degradation studies typically involve the exposure
5 of representative samples of drug substance or
6 drug product to the relevant stress conditions of
7 light, heat, humidity, acid/base hydrolysis and
8 oxidation. These experiments play an important
9 role in the drug development process.

10 The results of forced degradation
11 studies can facilitate drug formulation design,
12 in other words, sorting out your formulation such
13 that it's stable, what excipients one would
14 include to be sure that you have stable
15 formulation. And it's also used with solving of
16 stability-related problems.

17 Q. Dr. Davies, can you turn to tab 13 and 14
18 of your witness book, and there you will find JTX
19 75 and JTX 221. Can you identify those
20 documents?

21 A. Yes, these are the two documents that I
22 have just highlighted pages from, Alsante and the
23 Aubry reference.

24 MS. JACOBSEN: Your Honor,

1 plaintiffs move to introduce into evidence JTX 75
2 and JTX 221.

3 MR. BROWN: No objection.

4 THE COURT: Admitted without
5 objection.

6 MS. JACOBSEN: For the record,
7 Dr. Davies referred to Alsante as JTX 75 at page
8 60, and JTX 221, that's the Aubry reference, at
9 page 141.

10 BY MS. JACOBSEN:

11 Q. Dr. Davies, have you conducted stress
12 tests prior to your involvement in this case?

13 A. Yes, I have.

14 Q. Can you give me a simple example?

15 A. The example I conducted such test at both
16 the university and also at Molecular Profiles, for
17 example, recently we were working on a new drug
18 that we were helping to prepare the drug for the
19 formulation for a clinical trial. The drug is
20 acid labile, the stress test we saw that it was
21 acid labile and through further stress tests we
22 were able to use those stress tests to look at
23 the most appropriate pH modifying excipient to
24 use within that formulation.

1 Q. Dr. Davies, what does it mean to be acid
2 labile?

3 A. It means that the drug degrades in a
4 particular environment, such as say for example
5 in your stomach is an acidic environment. The
6 drug degrades in the acidic environment so we
7 include excipients such that they would help
8 stabilize the drug by acid modifying.

9 Q. I would like you to take a closer look at
10 the Alsante reference that you discussed a moment
11 ago. Can you generally describe what this paper
12 is about?

13 A. Yes. The Alsante paper was a stress
14 testing benchmarking study, and the authors say
15 to better understand current stress testing
16 practices in the pharmaceutical industry, the
17 authors conducted a benchmarking survey to which
18 twenty pharmaceutical companies responded. And
19 the authors themselves are from the
20 pharmaceutical industry, they're from Pfizer and
21 they're also from Eli Lilly.

22 Q. Does this paper discuss the use of stress
23 tests to study oxidative degradation?

24 A. Yes, it does. It has a section on

1 oxidation, and that section shown again on this
2 page on the slide, here we see that under
3 oxidation it says nineteen companies perform
4 oxidative stress testing on the drug substance.
5 Approximately 65 percent perform oxidative, which
6 I think is about 13, perform oxidative stress
7 testing on the drug product.

8 So that's both on the drug substance
9 and on the drug product. If you look below, it
10 shows here, that a range of conditions are used,
11 a range of conditions are used or, it shows that
12 you could use peroxide, use radical initiator,
13 pressurized oxygen, transition metal and bubbled
14 oxygen.

15 When you look at below in the figure
16 six from the paper, it shows that those
17 companies, it shows the peroxide, the typical
18 peroxide used is hydrogen peroxide, and it shows
19 a range of typical concentrations, study duration
20 and temperatures are used by those 19 companies.

21 So it's illustrating there are a
22 number of ways that one could conduct oxidative
23 stress tests. But the objective is the same in
24 all cases, it's to create an oxidative

1 degradation environment that one could study for
2 the drug.

3 Q. Why is it the object

4 Q. Why is that the objective to create an
5 oxidizing environment?

6 A. Such that one can study the oxidative
7 degradation of the drug and of the drug products
8 that's recited here.

9 Q. And why does the variability exist?

10 A. Variability exists because each drug is
11 different. Each drug has different
12 physicochemical properties and drugs undergo --
13 and kind of undergo oxidative degradation in
14 different ways.

15 So the scientist within the
16 pharmaceutical industry designed their
17 experiments in a way with an understanding that
18 each drug is different. And they designed their
19 experiments such that they're able to -- that's
20 why there is this variability.

21 And they design their experiments.
22 But in each case, it's the same objective. Its
23 objective -- the goal is the same, to be able to
24 create an oxidative environment, study the

1 oxidative degradation of the drug or the drug
2 product.

3 Q. Is any particular level of oxidative
4 degradation necessary to conduct a stress test?

5 A. Once you achieve a sufficient level such
6 that you're able to monitor the key degradation
7 products over the time scale of the experiment.

8 So, in my particular stress test, I wanted to
9 achieve sufficient degradation such that I was
10 able to distinguish between the samples which had
11 a -- control samples which had no acetaldehyde
12 present and the samples which had acetaldehyde
13 present, to be able to distinguish between those
14 two.

15 Q. What if there isn't enough degradation to
16 distinguish between the two samples?

17 A. If you don't generate enough oxidative
18 degradation of the sample then you can't make the
19 -- you can't undertake the experiments to -- to
20 distinguish between these two sets of samples in
21 this head-to-head stress test.

22 Q. And is the variability in the ways that
23 stress tests can be conducted recognized in the
24 Alsante reference?

1 A. Yes, it is. The point goes to the
2 conclusion. It says, Although the benchmarking
3 survey shows significantly diversified approaches
4 among the participating companies, the diversity
5 is not as great as one might expect based on the
6 lack of clear guidance in literature or in
7 regulatory guidelines.

8 What that's basically saying is that
9 the benchmarking survey is recognizing that there
10 is this diversified approach, but ultimately, the
11 scientists within the pharmaceutical industry
12 that design the experiments within these
13 parameters, because the differently -- because
14 there are all types of differences and you have
15 to tailor your test to the different drugs.

16 Q. Does Alsante discuss the stress test to
17 study the effect of potential antioxidants?

18 A. Yes, it does. Not -- sorry, not
19 explicitly, I should say, but it does talk about
20 the fact that one can undertake stress testing,
21 look at pharmaceutical formulations.

22 So, in addition, it says stress
23 testing can help in the selection of more-stable
24 drug substances, salt forms and drug

1 formulations. Well, what that's talking about
2 there are excipients. And if one looks at Figure
3 1 shown here, it shows that there is a -- here it
4 shows predominant reasons for performing the
5 stress test studies and it showed here
6 preformulation and excipient compatibility.

7 Seventeen of twenty companies use
8 stress testing to test the effect of an excipient
9 compatibility on the drug. And what it's talking
10 about there

11 is that one could use that -- exactly that
12 approach to study the effect of an antioxidant on
13 a drug or an excipient, for that matter.

14 MS. JACOBSEN: For the record, the
15 portions of Alsante that Dr. Davies referred to
16 in the previous set of slides occur at JTX 75 on
17 Pages 60, 64, 67, 68 and 72.

18 BY MS. JACOBSEN:

19 Q. Dr. Davies, does the FDA issue guidance on
20 how to perform stress tests?

21 A. It does. It's very general guidance and I
22 think that's recognized and cited in this Aubrey
23 paper, which I've highlighted on the next slide.
24 And that recognizes this, although it's FDA

1 guidance. And ICH guidelines provide useful
2 definitions and general comments about forced
3 degradation studies there.

4 And forced degradation studies are
5 another term for stress tests. Their direction
6 concerning the scope, timing and best practices
7 is very general and lacking in details.

8 That's recognizing what we saw in
9 Alsante, that there are a range of ways to
10 achieve -- that one can undertake stress tests
11 and achieve the same goal, the goal of studying
12 the oxidative degradation of the drug.

13 MS. JACOBSEN: For the record, Dr.
14 Davies referred to JTX 221 at Page 141.

15 BY MS. JACOBSEN:

16 Q. Dr. Davies, were you aware of Par ever
17 having performed a stress test?

18 A. Yes, I am. They undertook a stress test
19 when they -- they noticed in some accelerated
20 stability and long-term stability studies on their
21 products that prototype batches or other -- they
22 noticed the emergent degradation product.

23 Now, they -- they reasoned that that
24 degradation product was the product of an

1 oxidative degradation. So Par undertook a stress
2 test where they stressed Rivastigmine in an
3 oxidative environment. And they -- in doing so,
4 they identified the two key degradation products
5 that I highlighted in my schematic.

6 It showed that one of those key
7 degradation products was, indeed, the degradation
8 product that they were observing.

9 Q. Did 3M or Par use that test to determine
10 whether any compound was an antioxidant?

11 A. No, they didn't. But they could have
12 undertaken such a test because they created an
13 oxidative degradation environment and they could
14 have looked to see the effect of adding an
15 antioxidant to that environment.

16 Q. And can you please turn to Tab 15 of your
17 witness book? And there you'll find JTX 162.

18 Can you identify that document?

19 A. Yes. This is the work undertaken by 3M,
20 Par's manufacturer where they -- this is a
21 portion that includes the stress test.

22 MS. JACOBSEN: Your Honor,
23 plaintiff's move to introduce into evidence JTX
24 162.

1 MR. BROWN: No objection.

2 THE COURT: Admitted without
3 objection.

4 BY MS. JACOBSEN:

5 Q. Dr. Davies, I'd like you to turn now to
6 the detail of your stress test. And can you
7 please give us an overview of your stress test?

8 A. Yes. This is a very simple,
9 straightforward schematic which illustrates what
10 I've done here in creating an oxidative
11 environment for Rivastigmine by adding an
12 oxidizing agent in with Rivastigmine.

13 I then split that stock solution
14 into two to create a control and create a sample
15 where I add acetaldehyde. I then split those
16 samples further into three and I labeled them
17 showing here one, two, three. C for control, A
18 for acetaldehyde samples.

19 And then I stressed them. I
20 stressed them at a particular temperature for
21 over a period of time.

22 Q. And did you analyze what was happening in
23 those samples?

24 A. Yes. I took samples at key time points

1 and measured the degradation products. And I
2 then compared the two sets of data. I compared
3 the degradation products of the drug levels in
4 control and compared that to the
5 acetaldehyde-added forms.

6 Q. And who designs the stress test you
7 conducted?

8 A. I did.

9 Q. And who carried out the stress test?

10 A. The stress test was carried out by
11 experienced scientists, Ph.D.-level scientists
12 with molecular profiles under my supervision.

13 Q. And is the exact stress test with the
14 combination of conditions used described in a
15 single published literature?

16 A. There is more -- there are many of such
17 tests, stress tests, but it does fall within the
18 framework of the parameters that we saw in
19 Alsante and the like.

20 So the conditions that I used, and
21 I'm going to explain, fall within the same
22 parameters that are used, range of parameters
23 that are used within the pharmaceutical industry,
24 as described -- as highlighted by Alsante.

1 Q. So I'd like to walk through the test
2 step-by-step now. What was the first step?

3 A. The first step was to create a stock
4 solution. And to create a stock solution, I
5 dissolved the Rivastigmine in a solvent ethyl
6 acetate. I added T-butyl hydroperoxide, the
7 oxidizing agent to that solution.

8 Q. And how many stock solutions did you
9 prepare?

10 A. I prepared a single stock solution. Now,
11 the reason I did that is because I wanted that
12 single stock solution to be the source of the
13 solutions for the entirety of my test. And the
14 reason I did that, I wanted to eliminate any
15 variability that may occur if I make multiple
16 solutions.

17 So all these samples come from that
18 single stock solution to eliminate any
19 variability that may occur by preparation of
20 multiple solutions.

21 Q. And how much Rivastigmine was present in
22 your test samples?

23 A. It was in the order approximately of .36
24 percent.

1 Q. And is that the same amount that's present
2 in Par's ANDA products?

3 A. No, it's not. When you're doing a stress
4 test, you use a concentration which is sufficient
5 for you to be able to monitor the oxidative
6 degradation of the drug. And I showed in my
7 preliminary test that using .36 percent was a
8 suitable level such that I could monitor the
9 oxidative degradation in the time scale of the
10 experiment and achieve significant amounts of
11 oxidative degradation such that I could undertake
12 this head-to-head stress test.

13 Par uses a different concentration
14 in their products because their products are
15 designed to achieve a therapeutic effect. But
16 therapeutic effect is important there.

17 So the amount that Par uses in its
18 product is determined by its need to produce the
19 therapeutic effect.

20 Q. You indicate on the slide there that you
21 added T-butyl hydroperoxide you added. Is that
22 also called TBHP?

23 A. Yes, it is.

24 Q. And what is TBHP?

1 A. TBHP is an oxidizing agent. It's a
2 hydroperoxide. And I included it in here to
3 create an oxidizing environment. I particularly
4 included TBHP and I selected TBHP because I
5 wanted to create an anhydrous oxidizing
6 environment.

7 The reason for that is that
8 Rivastigmine also undergoes hydrolysis in water.
9 So I wanted to be sure that I was only watching
10 monitoring, should I say, the oxidative
11 degradation of the drug.

12 To do that, I selected TBHP because
13 it's anhydrous. It's free from water.

14 Q. And could you also use hydrogen peroxide?

15 A. I think -- well, one could have done that
16 experiment, but I think it would not have been
17 the right experiment to do because you would have
18 had two competing degradation processes
19 occurring. You'd have hydrolysis as well as
20 oxidative degradation.

21 So I wouldn't have done that
22 experiment. That's why I did the experiment with
23 TBHP because I was able to do that in an
24 anhydrous environment.

1 Q. And why would you have two competing
2 degradation pathways if you had used hydrogen
3 peroxide?

4 A. Because hydrogen peroxide is not -- would
5 not be free from available -- free from water.
6 And, in that context, one would -- if one was
7 undertaking an analysis where there was water
8 present, one would see that there were not only
9 oxidative degradation occurring, but the presence
10 of hydrolysis occurring.

11 And I wanted to look just simply at
12 oxidative degradation and that's why I chose an
13 anhydrous environment.

14 Q. And what does anhydrous mean, Dr. Davies?

15 A. It's free from water.

16 Q. And how did you know that you could use a
17 peroxide as the oxidizing agent?

18 A. Because peroxide -- it's well known that
19 Rivastigmine undergoes oxidative degradation in
20 the presence of peroxides.

21 Q. Is there any evidence in the literature of
22 the use of peroxide in stress tests?

23 A. Yes, there is. I show in this slide a
24 number of examples.

1 Alsante talks about using peroxides.

2 Aubry talks about using peroxide concentrations.

3 Bianchini talks about using T-butyl hydroperoxide

4 the one that I used. And the U.S. patent, the

5 '498 patent talks about using T-butyl

6 hydroperoxide as well. So a number of these

7 papers talk about using peroxide.

8 MS. JACOBSEN: Your Honor,

9 plaintiffs move to introduce into evidence JTX 74

10 and JTX 77.

11 MR. BROWN: No objection, Your

12 Honor.

13 THE COURT: Admitted without

14 objection.

15 MS. JACOBSEN: And for the record,

16 Dr. Davies referred to JTX 74 at Column 5, Lines

17 61 to 65. JTX 75 at Pages 67 to 68. JTX 77 at

18 Pages 1,056 and JTX 221 at Page 149.

19 BY MS. JACOBSEN:

20 Q. Dr. Davies, how much TBHP did you use?

21 A. I used approximately 1.3 percent TBHP in

22 this solution.

23 Q. And why did you use that amount?

24 A. That was the amount that I saw in my

1 preliminary work that showed that I could --
2 could obtain sufficient levels of Rivastigmine
3 degradation for my test. It also falls within the
4 range that is cited within some of these
5 references, for example, the Alsante reference.

6 It talks about one to three percent
7 peroxide levels. So it falls within such ranges.

8 Q. Now, you also noted that you added TBHP
9 and Rivastigmine to ethyl acetate. Why did you
10 use ethyl acetate?

11 A. Again, because ethyl acetate is anhydrous.
12 Ethyl acetate is free from water.

13 I wanted to just purely look at
14 oxidative degradation, so I chose ethyl acetate
15 for that reason. So I dissolved Rivastigmine and
16 T-butyl hydroperoxide into ethyl acetate so I
17 would only be watching and observing the
18 oxidative degradation of Rivastigmine, not any
19 other process.

20 Q. Do you know what solvent 3M and Par used
21 in the stress test that we looked at a moment
22 ago?

23 A. It used the same, the ethyl acetate.

24 Q. What was the next step?

1 THE COURT: Ms. Jacobson, would this
2 be a convenient time to take a break?

3 MS. JACOBSEN: Yes, Your Honor.

4 THE COURT: All right. Let's take a
5 15-minute break. And could I just ask the
6 defendants, you know, I said at the pretrial
7 conference, I was familiar with Dr. Davies and
8 Dr. Klibanov, and so therefore, skip going
9 through their background.

10 If you could get me the CVs of your
11 three experts in advance of when they take the
12 stand, then when you admit them, maybe we could
13 skip over their backgrounds, too. Okay?

14 MR. BROWN: We can do that, Your
15 Honor.

16 THE COURT: All right. We'll be in
17 recess.

18 THE CLERK: All rise.

19 (A brief recess was taken.)

20 THE COURT: All right. You may all
21 be seated. For what it's worth I'm going to try
22 to go to about quarter of 1:00 for lunch. Okay?

23 MS. JACOBSEN: Thank you, Your
24 Honor.

1 THE COURT: Good ahead,

2 Ms. Jacobsen.

3 BY MS. JACOBSEN:

4 Q. Dr. Davies, before the break, we were
5 about to move to the second step in your stress
6 test. And can you please explain what that
7 second step was?

8 A. Yes. The second step was to separate that
9 stock solution into two parts. So the one I'm
10 going to -- I have as a control one half I have
11 as a control, the other half I have as the
12 acetaldehyde. And the way I do that is that I
13 dissolved acetaldehyde in the ethyl acetate
14 solvent and I add it back to this half of the
15 stock solution.

16 I then created a control by adding
17 exactly the same amount of the solvent, ethyl
18 acetate to the control so I maintained the
19 concentrations between the two samples and the
20 only difference between the two samples is the
21 presence or absence of acetaldehyde.

22 Q. How much acetaldehyde did you add to the
23 test samples?

24 A. I added approximately 0.0017 percent by

1 weight to the second mixture.

2 Q. What is the relevance of that amount of
3 acetaldehyde in your stress test?

4 A. That is the level that was reported in
5 Par's ANDA product, that's the reason why I chose
6 that particular level.

7 Q. What was the next step?

8 A. I then separated each of the controls into
9 three separate samples, label them C1, C2, C3.
10 And I did the same for the acetaldehyde, I
11 separated them into three samples labeling, A1,
12 A2, A3.

13 I did that because I wanted to be
14 sure that I was creating a statistically
15 significant test so I could monitor the effect in
16 triplicate measurements for each sample, so that I
17 had undertaken an appropriate statistically
18 significant experiment.

19 Q. And what did you do next?

20 A. What I did next is then I stressed those
21 samples. And I stressed those samples at 60
22 degrees centigrade.

23 Q. Why did you use an elevated temperature?

24 A. I used an elevated temperature because in

1 preliminary experiments I had looked at room
2 temperature, I looked at 40 degrees, I looked at
3 60 degrees, and I chose to use 60 degrees because
4 that gave me the greatest amount, the largest
5 amount of the oxidative degradation of the drug.

6 As you increase the temperature, you
7 increase the rate at which the drug degrades, so
8 over the time period of my experiment I was
9 getting more degradation with the higher
10 temperature than I was at 40 and with room
11 temperature, and that's why I chose 60 degrees.

12 Q. Could you have used room temperature or 40
13 degrees Celsius for your stress test?

14 A. I could have, but that would taken longer,
15 and the point of the stress test is that one can
16 look at -- one can increase the rate of that
17 degradation and look at it over a shorter period
18 of time. The same mechanism, the same
19 chemistries occur, although it's just occurring
20 slower at lower temperatures, so you're seeing
21 the same degradation product.

22 Q. Did you see enough degradation product at
23 room temperature at 40 degrees Celsius to run the
24 stress test in the time that you conducted your

1 stress test at?

2 A. I didn't think so, and that's why I chose
3 the 60 degrees. I thought 60 degrees would be
4 over the time frame that I wanted to run the
5 experiment, and I thought that was appropriate, I
6 thought it was sufficient at 60 degrees.

7 Q. Why was it appropriate to use a
8 temperature that generated sufficient
9 degradation?

10 A. Over the time scale of the experiment
11 because I used that temperature, I saw as I will
12 show you, I saw the same two key degradation
13 products that one sees for oxidative degradation
14 of rivastigmine, and I saw them in sufficient
15 amounts over the time period of the experiment
16 such that I could then compare the levels of
17 those degradation products in the control sample
18 without acetaldehyde and the samples with
19 acetaldehyde, certain level you had to undertake
20 that head to head stress test.

21 Q. Could you have done that comparison if you
22 had not seen sufficient levels of degradation?

23 A. No, I could not have done that.

24 Q. And why not?

1 A. Because if you don't see sufficient levels
2 of degradation, then you can't deduce whether or
3 not that this head to head study, the only
4 variable that's changing, the presence or absence
5 of acetaldehyde, and you wouldn't be able to
6 distinguish that affect whether or not
7 acetaldehyde did indeed have an affect, did
8 indeed prevent the oxidative degradation, you got
9 to induce oxidative degradation before you can
10 see the effect of reducing it.

11 Q. Are there examples in the literature of
12 the use of peroxides at 60 degrees Celsius in
13 stress tests?

14 A. There is a range of temperatures in the
15 literature and 60 degrees falls within those
16 ranges. So, for example, Alsante talks about
17 peroxide stress testing ranging from room
18 temperature to greater than 50 degrees
19 centigrade. The Bianchini testing talks about
20 room temperature up to 100 degrees centigrade.
21 Singh talks about peroxide stress testing up to a
22 hundred degrees centigrade. And the US patent
23 '498 talks about taking stress testing up to
24 around 60 degrees centigrade.

1 Q. And what oxidizing agent was used at 60
2 degrees Celsius in the '498 patent?

3 A. It's the same, the TBHP, the hydroperoxide
4 that I used.

5 MS. JACOBSEN: Your Honor,
6 plaintiffs introduce into evidence JTX 78.

7 MR. BROWN: No objection, Your
8 Honor.

9 THE COURT: Admitted without
10 objection.

11 MS. JACOBSEN: For the record,
12 Dr. Davies referred to JTX 74 in column five
13 lines 61 to 65, JTX 75 at page 68, JTX 77 at
14 pages 1056 and 1058, and JTX 78 at page four.

15 BY MS. JACOBSEN:

16 Q. What was the next step, Dr. Davies?

17 A. The next step, once I incubated my
18 samples, stressed them at 60 degrees C, I then
19 took samples at key time points. I took samples
20 at three time points, 6, 15 and 21 hours. I took
21 the samples of those time points because I wanted
22 to see what was happening to the oxidative
23 degradation over a period of time. I wanted to
24 see how the level of the degradation product was

1 changing as the function of time, over the time
2 scale of my experiment.

3 I then wanted to see whether or not
4 acetaldehyde had any influence over that as a
5 function of time. My experiment was designed,
6 the only differences, the presence of
7 acetaldehyde.

8 So is acetaldehyde reducing the level of
9 oxidative degradation products at 6, 15 and 21
10 hours across the board, that's what I wanted to
11 see.

12 Q. Why did you choose those time points?

13 A. Those time points allow me to as I say,
14 watch the change in the levels of the oxidative
15 degradation as a function of time. They also
16 allowed me to undertake a good statistical
17 analysis of my data.

18 Q. And did you conduct any preliminary stress
19 testing to determine whether those were
20 appropriate time points?

21 A. Yes, I did. In my preliminary test, I
22 looked at the -- I looked at I think up to around
23 14-and-a-half hours, and after -- with the three
24 different temperatures, and I showed that up to

1 that time point I was getting sufficient
2 degradation, so these three time points were good
3 to use for my stress test as I will go on to
4 show.

5 Q. Are there examples in the literature of
6 stress tests conducted over this time period?

7 A. Yes, there are. So Alsante talks about
8 maximum duration ranging from a day to seven
9 days. Bianchini talks about stressing anywhere
10 from 7.2 hours to 30 days. Singh talks about the
11 API was stressed typically between one and 24
12 hours, so the time frame that I'm looking at is
13 typical of what would be employed by scientists
14 undertaking a stress test.

15 MS. JACOBSEN: For the record,
16 Dr. Davies referred to JTX 75 at pages 67 to 68,
17 JTX 77 at page 1058, and JTX 78 at page four.

18 BY MS. JACOBSEN:

19 Q. And what did you do with the samples that
20 you collected at each time point?

21 A. What I did was I then used the technique
22 of high performance liquid chromatography. High
23 performance liquid chromatography is a standard
24 technique used in the pharmaceutical industry to

1 separate and to identify and quantify the level
2 of drug and drug degradation product.

3 Q. How does HPLC work?

4 A. HPLC or high performance liquid
5 chromatography, this is very simple schematic to
6 illustrate the point and I'll show a little video
7 related to that.

8 You have a test sample, your test
9 sample contains a mixture of compounds. That's
10 injected into the HPLC system where it's carried
11 along by fluid into an HPLC column. The HPLC
12 column is designed to separate different
13 components of the mixture. And these will come
14 and pass through the column depending on how they
15 interact with the column at different rates.

16 And then, they will be separated,
17 come off the column and be detected in some way.
18 In this case, I have used light, UV lights as a
19 detection. And then what you see, you see is a
20 chromatogram where the chromatogram is time as a
21 function of coming off the column, and then
22 detection is the level of detection in the UV
23 detector.

24

1 A. And the time at which it comes off the
2 column helps to identify the compounds as the
3 level of detection, also helps you to understand
4 how much is present in the sample. So if we run
5 them in the video, here's a mixture. It separates
6 it.

7 One comes off the column. You see
8 it in this chromatogram. Next one comes off the
9 column. You see it in the chromatogram.

10 Finally the last one comes off the
11 column the slowest. You see this in the
12 chromatogram. As I said, we can use the position
13 that it comes off the column to help identify
14 compounds.

15 We can use also the amount, the area
16 or the peak helps you establish how much is
17 present, sorry, coming off the column.

18 Q. And what did your HPLC results look like?

19 A. This is an example of an HPLC printout and
20 it's taken from, excuse me, Control-2 sample at
21 21 hours. And here we have the chromatogram. We
22 have time along here in minutes, time it takes to
23 come off the column.

24 We have the response of the

1 detection shown here. We have three main peaks
2 that I've highlighted.

3 The main peak in the center here is
4 Rivastigmine. We're actually looking at the base
5 of the peak. The peak actually extends beyond
6 what I've shown here.

7 And on the side of that, we have a
8 peak here, which is Impurity 4. There's a peak
9 here, which is ECAV.

10 Now, how do I know each one of those
11 is other chemicals that I've stated? Well, I
12 have a standard for Rivastigmine and that
13 standard comes off of this time point.

14 I also was able to obtain a standard
15 for Impurity 4. And that, again, comes off --
16 the standard came off of this time port. So
17 that's the standard where the scientists within
18 the pharmaceutical industry use to establish the
19 identity of the peak in this way.

20 I also then looked at this peak. I
21 didn't have a standard for ECAV.

22 ECAV is -- excuse me. What I was
23 able to do is take a UV spectrum of the compounds
24 in that peak and the UV spectrum was identical to

1 the same UV spectrum undertaken by Par and their
2 scientists. So that demonstrated to me that this
3 was ECAV.

4 Now, this is one of my typical HPLC
5 printouts and I just want to point something out.
6 I'm seeing the drug and I'm seeing the two key
7 degradation products in my stress test.

8 And the point of that -- this is the
9 control and the point's sample. And the point I
10 want to make is I've replicated what is known
11 about the oxidative degradation of Rivastigmine.

12 I've replicated this in a way that
13 I've identified the two key degradation products
14 of Rivastigmine. So, in my stress test, I'm
15 replicating what is known, the known mechanism
16 for oxidative degradation of Rivastigmine.

17 Q. And the Rivastigmine and Impurity 4
18 standards that you referred to, was that
19 something you were able to purchase?

20 A. That's correct.

21 Q. And do you understand that Dr. Ganem has
22 asserted that other compounds could have been
23 formed by side reactions with TBHP in your stress
24 test?

1 A. That's correct.

2 Q. And do you agree?

3 A. I don't. Dr. Ganem doesn't go -- doesn't
4 tell us what those compounds are equally. And
5 I've shown in my test and my results. I've
6 shown that I've identified two key degradation
7 products of -- for the known -- for Rivastigmine
8 undergoing oxidative degradation.

9 But I also undertook a mass-balance
10 analysis where I, through that mass-balance
11 analysis, that these three peaks account for over
12 99 percent of the peaks that come off the column.
13 That demonstrates to me that I am looking at the
14 two key degradation products and the drug in this
15 analysis.

16 And as I will show you, those two
17 key degradation products change as a function of
18 time in a manner which is consistent with the
19 oxidative degradation of Rivastigmine. So I
20 don't think there's any basis for Dr. Ganem's
21 position there could be other key degradation
22 products formed. In fact, he doesn't identify
23 what those are.

24 Q. And when you ran your stress test, what

1 did you observe?

2 A. When I ran my stress test, what I observed
3 that, as a function of time in the control
4 samples, the key degradation products increased
5 as a function of time. When I compared those
6 samples, control samples to the samples that
7 contain acetaldehyde, I saw that, as a function
8 of time, less of these impurities in degradation
9 products were formed.

10 That demonstrates to me -- and I
11 quite want to show statistically -- there's a
12 statistical significance between the control and
13 the acetaldehyde samples demonstrating that
14 acetaldehyde is reducing the oxidative
15 degradation of Rivastigmine.

16 Q. And --

17 A. I have a little figure to demonstrate
18 that. Okay.

19 So this is the start point. And at
20 the start point, you see there's the peak for
21 Rivastigmine here. And I'm going to -- in this
22 short video, I'm going to show -- I'm going to
23 show the control samples in orange and the
24 acetaldehyde samples in purple.

1 And for the purpose of this, I'm
2 just going to overlay them, so you can see how
3 they rise as a function of time. So if we start
4 the video when you're ready.

5 If we go up, the -- the sample is
6 taken up to the first time point at six minutes.
7 And you see that there's a rise in the levels of
8 these two impurities.

9 And the rise in the level of the two
10 impurities is different for the control samples
11 relative to the samples with acetaldehyde. The
12 acetaldehyde samples are shown in purple. The
13 control samples are shown in orange.

14 And you see that the control samples
15 are higher than the levels reported for the
16 samples with acetaldehyde actually if you look at
17 the level of Rivastigmine. There's more
18 Rivastigmine present in the sample shown here
19 with acetaldehyde than there is without
20 acetaldehyde.

21 If we continue onwards, this goes on
22 to the 15-hour mark. And, again, you're seeing
23 the same effect. You're seeing the difference
24 becoming more pronounced.

1 You're seeing the level of the
2 control are higher than that for the two key
3 degradation products that acetaldehyde -- you're
4 also seeing when one looks at the drug, you're
5 seeing high levels of the drug relative to that
6 with acetaldehyde present and then without.

7 If one continues onwards to the
8 final time point, there's the 21 hours. You see
9 that stark difference between the two sets of
10 samples.

11 The control samples are higher in
12 terms of the two impurities relative to that
13 acetaldehyde sample. And the level of the drug
14 is also higher, as one would expect, in the
15 acetaldehyde sample, because the acetaldehyde
16 compound is reducing the oxidative degradation of
17 the drug.

18 Q. Thank you, Dr. Davies. I think you
19 misspoke when you said the first time point was
20 six minutes.

21 A. I thought I did. I apologize.

22 Q. Not at all. What was the first time
23 point?

24 A. I wondered if I had said minutes. It's

1 six hours.

2 Q. Thank you.

3 Dr. Davies, can you summarize your
4 test results?

5 A. Yes. This is a table where I tried to
6 summarize the results and it does show the
7 results.

8 These, I'm showing it in bar charts,
9 and I've done it for the six-hour time, the
10 15-hour time and the 21-hour time. And in
11 accordance with the bar chart for the six-hour
12 time, what I've done is I've added together the
13 percentages for the two key oxidative degradation
14 products.

15 And, again, I've cut -- color-coded
16 the two sets of samples. Orange is the control,
17 the without acetaldehyde.

18 The purple is the control -- is the
19 sample with acetaldehyde present in my
20 head-to-head study.

21 And I've given you the total
22 percentages here for comparison and I've done
23 that for each of the time points. And as you can
24 see, at each point, there's more of the

1 degradation compounds in the sample without
2 acetaldehyde in the control sample.

3 There's less degradation products in
4 each one of the samples with acetaldehyde. So
5 there's direct evidence. There's only one
6 variable occurring here, the presence or absence
7 of acetaldehyde.

8 And it's showing in each case at
9 each time point, there's less degradation
10 products in the samples with acetaldehyde.

11 Q. And approximately how much less is there
12 at each time point?

13 A. It's approximately 30 percent.

14 Q. Were you able to draw any conclusions from
15 your test results?

16 A. Yes. I was able to draw the conclusion
17 that acetaldehyde reduces -- is an agent which
18 reduces the oxidative degradation. It confirms
19 that acetaldehyde is an antioxidant.

20 Q. Did you measure whether there was any
21 acetaldehyde left in your test samples after six,
22 15 and 21 hours?

23 A. No, I did not.

24 Q. And how did you know the reduction in

1 oxidative degradation was due to acetaldehyde?

2 A. Well, I know it because the data shows me.

3 There's only one variable in play here, the

4 presence or absence of acetaldehyde. And I

5 designed the experiments in a way that I know

6 acetaldehyde is a known reducing agent. Reducing

7 agents can act as antioxidants.

8 My test clearly demonstrates that

9 acetaldehyde is an antioxidant.

10 Q. And Dr. Davies, there is a notation on

11 this slide, P less than 0.05 for all samples.

12 What does that indicate?

13 A. What that indicates is that one could look

14 at this data, as we have done, and you can

15 consistently see that looking at the bar charts

16 that there is always less in the samples with

17 acetaldehyde relative to the control. But you

18 can also undertake a statistical analysis. And I

19 undertook a statistical analysis to see whether

20 or not the data between these two sets of samples

21 at each time point, does it come from the same

22 population, or is it different. Can I say these

23 two sets of data are statistically different.

24 So I ran what is called a two sample

1 T-test. This is a standard test used to look at,
2 to see whether or not two samples are the same or
3 are they different. And I showed that -- the P
4 value here is the notation that's used. And I
5 showed with my data, related to the probability
6 and I showed in my data that there is 95 percent
7 confidence that these two sets of data are
8 different. So I have 95 percent confidence
9 levels that the samples without acetaldehyde, the
10 control samples, are different than the
11 samples with acetaldehyde.

12 Q. Do you understand that Par's expert, Dr.
13 Michniak-Kohn disagrees that your results are
14 statistically significant?

15 A. Yes, I understand that. I don't think
16 Dr. Michniak-Kohn disagreed with the use of the
17 T-test. She just disagrees with the way in which
18 I have undertaken that.

19 If we go to the next slide, I can
20 explain that.

21 I undertook this test where I had
22 used what is called a T-test, it's a one-tailed
23 T-test. What that means is that you have some
24 understanding of the test at the direction at

1 which the change may occur. So I had some
2 expectation that acetaldehyde would either not or
3 it would reduce the oxidative degradation of
4 rivastigmine.

5 Now, I based that on my knowledge of
6 the molecules -- of the reducing agent. That a
7 reducing agent's known to act as an antioxidant.
8 They reduce the level of oxidative degradation.
9 Dr. Michniak-Kohn suggested that well, you can't
10 assume that. She suggested that acetaldehyde
11 could not only reduce -- that it not only reduces
12 oxidative degradation, but it could increase the
13 oxidative degradation, the so-called two-tail
14 test.

15 I don't agree with that, but anyway
16 I undertook that test. One undertakes that test
17 where it could either decrease or increase the
18 oxidative degradation. I get values of 90 --
19 greater than 90 percent confidence that the two
20 sets of data are statistically significantly
21 different.

22 Q. And what does that mean if you have 90
23 percent confidence that the two data sets are
24 different?

1 A. It means that acetaldehyde is an
2 antioxidant for rivastigmine using that approach.

3 Q. Have you seen any evidence that
4 acetaldehyde can promote oxidative degradation?

5 A. No, I have not.

6 Q. Did you consider the Albano and McNesby
7 articles raised by Dr. Ganem?

8 A. Yes, I did.

9 Q. Does the Albano reference teach that
10 acetaldehyde promotes oxidation?

11 A. Well, this paper shows about the free
12 radical activation of acetaldehyde and its role
13 in protein alkylation. This is a process
14 occurring in vivo in the body. And the
15 acetaldehyde is oxidized using an enzyme,
16 xanthine oxidase. Xanthine oxidase is a
17 particular enzyme in the body that is known to
18 change compounds such as acetaldehyde. And in
19 the case of acetaldehyde forms -- that occurs in
20 the body as an important process that occurs in
21 the body in vivo. There is no xanthine oxidase in
22 my test and there are no such conditions in my
23 test.

24 Q. What about the McNesby article?

1 A. Yes, the McNesby article talks about when
2 exposed to oxygen or air, an aldehyde is slowly
3 oxidized to the corresponding peracid which
4 further reacts with the aldehyde to form the
5 normal acid and the peracid. But if you read
6 further into the article, it talks about Kagan
7 and Lubarksy were the first to isolate a complex
8 using acetaldehyde and peracid, and their
9 complex were stable at minus 30 degrees
10 centigrade and decomposed to normal acid that
11 would be acetic acid on heating or on treatment
12 with catalyst.

13 So the point is this peracid of
14 acetaldehyde is only stable at minus 30 degrees
15 centigrade, it only exist at that temperature it
16 doesn't exist at temperatures at say above that,
17 so it's not relevant to this particular case.

18 Q. And is minus 30 degrees Celsius, do you
19 know what that is in Fahrenheit?

20 A. I think it's -- I'm not really good on
21 Fahrenheit, but I think it's around minus 20. Is
22 that right? I'm not very good at that.

23 Q. If we go back to your statistical
24 analysis, what happens if you run a two-tailed

1 T-test?

2 A. So if you run the two-tailed T-test, so if
3 you run this two-tailed T-test where you don't --
4 you assume you go either reduce oxidation or
5 increase oxidation, you get a confidence of
6 greater than 90 percent that acetaldehyde is an
7 antioxidant for rivastigmine.

8 Q. There is a reference there to unequal
9 variance. What is that?

10 A. Yes, Dr. Michniak-Kohn suggested that I
11 couldn't assume that the two sets of samples have
12 equal variance. And here variance relates to
13 this is a statistical term. It relates to the
14 variation of the data around the mean.

15 Now, I actually set up my experiment
16 in such a way that I used the same number of
17 samples in each data set. I also only had one
18 variable changing, the presence or absence of
19 acetaldehyde. In such circumstances the use of
20 equal variance is appropriate.

21 However, I did calculate based on
22 the two-tailed test using unequal variance what
23 the confidence would be, and it showed that the
24 confidence would range from 87 to 94 percent

1 confidence that acetaldehyde is an antioxidant
2 for rivastigmine.

3 Q. Did you confirm whether your assumption of
4 equal variance was appropriate?

5 A. Yes. I did a further test called the
6 statistical test called the F-test. Using the
7 F-test you can test whether or not two sets of
8 samples, whether the variances are equal or
9 different. And again, using the F-test I was
10 able to show that, in fact, the two sets of
11 samples had equal variance.

12 Q. Did you draw any conclusion from that?

13 A. Yes. Sorry. I drew the conclusion that
14 my use of equal variance is appropriate, and it
15 showed that I was getting, even if I used the
16 two-tail test which I don't think is appropriate,
17 I was getting 90 percent or greater confidence
18 that acetaldehyde is an antioxidant for
19 rivastigmine.

20 Q. Did you conduct any other statistical
21 analysis on your data?

22 A. I did. Then I went on to use the
23 technique used linear regression analysis. In
24 linear regression analysis it looks at the rate

1 in which the two sets of samples form the key
2 degradation products. And it compares those
3 rates using residuals. And when you use that
4 approach, I found that I had greater than 99
5 percent confidence that acetaldehyde is an
6 antioxidant for rivastigmine, whether I used a
7 one-tail or a two-tail approach.

8 Q. Dr. Davies, can you please turn to tab 19
9 in your witness book. And there you will find
10 JTX 66.

11 A. Yes. That's appendix E from my opening
12 report, describing my stress test.

13 MS. JACOBSEN: Your Honor,
14 plaintiffs move to introduce JTX 66 into
15 evidence. I believe there was an objection, but
16 I think we have resolved it.

17 MR. BROWN: Yes, Your Honor, we will
18 not object to this coming in for the data that's
19 in it as long as it doesn't come in for the
20 opinions that are provided in it. And we have
21 conditioned that on Novartis also introducing
22 into evidence an underlying laboratory notebook
23 and some underlying raw HPLC data, as long as it
24 all comes in.

1 THE COURT: So basically the numbers
2 are in, the opinions are not.

3 MR. BROWN: Correct.

4 THE COURT: Okay. It's admitted
5 with that stipulation.

6 MS. JACOBSEN: Thank you, Your
7 Honor.

8 MS. JACOBSEN: Thank you, Your
9 Honor.

10 BY MS. JACOBSEN:

11 Q. And, Dr. Davies, can you turn to Tab 20 in
12 your witness book? And there you'll find PTX
13 103.

14 A. Yes. That's my laboratory notebook and
15 also some -- the HPLC column chromatograms
16 column.

17 Q. Is that the data underlying stress tests
18 and the data in Appendix E that we just looked
19 at, JTX 66?

20 A. That's correct.

21 MS. JACOBSEN: And, Your Honor,
22 plaintiff would move to introduce into evidence
23 PTX 103.

24 MR. BROWN: No objection.

1 THE COURT: Admitted without
2 objection.

3 BY MS. JACOBSEN:

4 Q. And then, Dr. Davies, can you please turn
5 to Tab 43 of your witness book? It should be the
6 last tab.

7 And you should have JTX 170.

8 A. Yes.

9 Q. Do you recognize that document?

10 A. This is my laboratory notebook.

11 MS. JACOBSEN: And, Your Honor,
12 plaintiffs move to introduce JTX 170 into
13 evidence.

14 MR. BROWN: No objection.

15 THE COURT: Admitted without
16 objection.

17 BY MS. JACOBSEN:

18 Q. And then, Dr. Davies, can you please turn
19 to Tab 21 of your witness book? And there you'll
20 find PTX 365.

21 A. Yes. This is the -- this is a copy of the
22 slide that we were just looking at of the stress
23 test confirming acetaldehyde is an antioxidant.

24 MS. JACOBSEN: And, Your Honor,

1 plaintiffs move to introduce into evidence PTX
2 365.

3 MR. BROWN: Your Honor, we object to
4 this as an improper summary. It contains, among
5 other things, opinions about the list of
6 statistical significance. And the way the data
7 is presented, we move is argumentative.

8 And while we wouldn't object to a
9 proper summary, but we do object to this data.

10 THE COURT: Ms. Jacobsen.

11 MS. JACOBSEN: It's a summary chart
12 of and you see a great deal of numbers and raw
13 data that are provided in Dr. Davies' Appendix E
14 from his report. The data is just reporting the
15 numbers, and the statistical notation is
16 reporting the results of Dr. Davies' test.

17 THE COURT: All right. Well, I'm
18 going to sustain the objection. I will submit it
19 as a court exhibit, so there is a demonstrative
20 exhibit in the record.

21 It seems to me that Dr. Davies has
22 essentially testified at one time or another to
23 all of these numbers, so I think, I don't know,
24 by not having this as an exhibit, I don't think

1 you're actually losing anything.

2 MS. JACOBSEN: We haven't read all
3 the percentages into the record and that would be
4 a way of providing all of those percentages to
5 the Court.

6 MR. BROWN: Your Honor, the
7 Appendix E exhibit that we talked about a minute
8 ago provides all of the data and in a convenient
9 chart form. This is not providing a summary of
10 the data.

11 The data is readily readable within
12 that document.

13 THE COURT: I presume you've looked
14 and saw the numbers that are actually in this
15 exhibit that are, in fact, reflected in the
16 record somewhere.

17 MR. BROWN: I believe. Well, the
18 numbers that are not reflected in the record
19 somewhere are the totals, the 2.49 and the 3.55.
20 He didn't provide those in his report.

21 THE COURT: That's the total. But,
22 for example, the 2.49, the 1.57 and the 0.92 are
23 in the record?

24 MR. BROWN: Those are in the record.

1 THE COURT: I can understand I can
2 get the 2.49 from those two numbers. Okay. So I
3 think we're arguing about something that's
4 actually not terribly important here.

5 So let's move it on. But I will
6 sustain the objection to it coming in as having
7 some independent value.

8 MS. JACOBSEN: Thank you, Your
9 Honor.

10 BY MS. JACOBSEN:

11 Q. So, Dr. Davies, before we move on, can you
12 briefly summarize your opinions with respect to
13 the first issue, which is whether acetaldehyde is
14 an antioxidant?

15 A. Yes. I believe acetaldehyde is an agent
16 which reduces oxidative degradation.

17 I believe my test has shown that and
18 I believe acetaldehyde is an antioxidant. That
19 confirms the literature that I have cited in
20 terms of acetaldehyde being a reducing agent.
21 Reducing agent is a known antioxidant.

22 Q. Dr. Davies, did you perform any stress
23 testing on Par's ANDA products?

24 A. No, I did not.

1 Q. Why not?

2 A. I was not able to do that because, in my
3 test, I was able to perform a head-to-head test
4 where there's only one variable change. But in
5 Par's ANDA products, I wasn't able to obtain a
6 product where I was able to compare products with
7 and without acetaldehyde where that was the only
8 variable that they would be changing.

9 Q. And why were you not able to obtain that
10 product?

11 A. Because I wasn't able to obtain products
12 where they were adhesive, for instance, with and
13 without acetaldehyde. I wasn't able to obtain
14 those products.

15 I was also not able to make the
16 products. The only people who could actually
17 make those products is Par with or without the
18 presence of acetaldehyde, keeping everything else
19 the same.

20 Q. And, Dr. Davies, did you consider Par's
21 stability data relating to the ANDA products?

22 A. I did.

23 Q. And what data did you consider?

24 A. I considered the data performed, their

1 accelerated stability and also their long-term
2 stability studies on their batches.

3 Q. And which batches did you consider?

4 A. There were nine of them. One of the
5 batches, they didn't test for acetaldehyde.

6 There were two of the batches where
7 it was said there is none detected meaning below
8 limits of detection of acetaldehyde. And there
9 was six batches where they did detect
10 acetaldehyde.

11 Q. And what do you understand Par's position
12 to be with respect to this data?

13 A. I believe Par's position is -- I believe
14 their expert, Dr. Buckton believes that if you
15 compare the level of the degradation products in
16 Par's ANDA batches, those batches which contain
17 no acetaldehyde and compared to the levels of
18 degradation products with those that do contain
19 acetaldehyde, he believes you can conclude that,
20 in fact, acetaldehyde is not an agent to reduce
21 oxidative degradation.

22 Q. And you mentioned batches of Par's ANDA
23 products where there was no acetaldehyde?

24 A. Sorry. Non-detectable.

1 Q. And do you agree with Dr. Buckton's
2 opinion with respect to this data?

3 A. I don't because I don't think you can make
4 that determination. There are two reasons why I
5 believe that's the case.

6 The first reason is important is
7 that you can't set up this head-to-head study
8 where the only variable changing is acetaldehyde.
9 There's nine different batches.

10 The different components of those
11 batches, the dry adhesive, the tackifier, et
12 cetera, there's no batch that's made with the
13 same components. Different -- different lot
14 numbers are used. Different lots of the
15 components are used to make those batches.

16 Because of that batch-to-batch
17 variation in the lots used for the different
18 components, there are other variables in play.
19 So, therefore, you can't say, based on that,
20 that -- you can't exclude the effect of other
21 components on the degradation properties that are
22 formed.

23 Q. And can you illustrate that point by
24 reference to the next slide?

1 A. Yeah. I have a slide which illustrates
2 that point.

3 This is a very bright, colorful
4 slide, but I've done it to illustrate a point.
5 What I've done is that I've shown here the ANDA
6 batch numbers shown here. And on the right-hand
7 side, I'm showing this is the batch where
8 acetaldehyde was not tested.

9 There's a line drawn and then
10 there's two batches here. These are batches
11 where acetaldehyde is not detected.

12 And then, finally, below that
13 further line, these are the batches where
14 acetaldehyde is detected. Now, what I've done,
15 I'm just showing here the backing layer, the
16 drug-in-adhesive layer and the release liner.

17 And within the drug-in-adhesive
18 layer, I'm showing three key components: The
19 adhesive, the Rivastigmine, the tackifier.

20 And what I've done is I'm showing
21 here lot numbers of the components. I'll
22 highlight on the drug adhesive layer.

23 And I've given each lot number, a
24 combination of lot numbers or different color.

1 And if you just look at the colors to illustrate
2 the point, no batch is made with the same
3 combination across the board for the backing
4 layer right through the release liner.

5 No batch is made with the same
6 combination of colors. And that illustrates the
7 point. There's batch-to-batch variability in the
8 lots that are used to manufacture the product.

9 So, for this reason, that one cannot
10 -- and it's for this reason that one cannot use
11 -- rule out the effect on the variation in the
12 lots used to manufacture the product of the data.

13 Q. And, Dr. Davies, can you please turn to
14 Tab 24 of your witness book. You'll find PTX
15 364.

16 A. Yes. This is the table from which these
17 lot numbers are drawn. And that's correct.

18 MS. JACOBSEN: And, Your Honor,
19 plaintiff's move to introduce into evidence PTX
20 364.

21 MR. BROWN: No objection.

22 THE COURT: Admitted without
23 objection.

24 MS. JACOBSEN: And for the record,

1 Dr. Davies is referring to PTX 364 discussing the
2 batch variability. And the information on this
3 slide also comes from JTX 180, JTX 181, JTX 192,
4 JTX 197, JTX 198, JTX 199, PTX 352 and PTX 353.

5 BY MS. JACOBSEN:

6 Q. And, Dr. Davies, why was the
7 batch-to-batch variability relevant to your
8 analysis?

9 A. It's relevant to my analysis because of
10 that batch-to-batch variability. You cannot
11 conclude from the stability data that
12 acetaldehyde is not an agent that reduces
13 oxidative degradation.

14 Because of this batch-to-batch
15 variability, there are multiple variables at play
16 here. So, for that reason, you cannot draw that
17 conclusion.

18 Q. And is there any batch in which
19 acetaldehyde was not detected that is made with
20 the same components as one made with one in which
21 acetaldehyde was detected?

22 A. Yes. If one looks at -- I'll show this,
23 if one looks at these top two batches, here, you
24 see --

1 Q. Dr. Davies, sorry to interrupt you, but I
2 think you misheard my question. Can we just go
3 back to the previous slide just so we're clear.
4 And I was asking you about the batches with
5 acetaldehyde not detected, and acetaldehyde
6 detected.

7 And is there any batch made with the
8 same components or any two batches made with the
9 same component one in which acetaldehyde was
10 detected and one in which acetaldehyde was not
11 detected?

12 A. There is no -- for these two sets, if we
13 look at the colors, it illustrates the point as I
14 have said before, that no batch has been made
15 with the same combination of lot numbers. That's
16 important. That's important because it shows
17 that there is batch-to-batch variable in the lots
18 that one uses, therefore, in the samples which
19 have been tested for acetaldehyde, therefore, one
20 cannot use this information -- there are other
21 variables that are going to be in play that can
22 influence the interpretation of the stability
23 data. It's not a direct head-to-head comparison.

24 Q. Thank you, Dr. Davies.

1 And other than the batch-to-batch
2 variability, is there any other reason that you
3 disagree with Par's position regarding its
4 stability data?

5 A. Yes. If one looks at -- I was going to
6 talk about it. If one looks at these two, top
7 two patches, if we move to the next slide I'll
8 explain it. If you look at these top two
9 patches, these are patches which are produced
10 wherein this case they do have the same
11 combination of lots for the drug-in-adhesive
12 layer, all be it, that one of them, acetaldehyde
13 was not tested.

14 Now, if you look at the stability of
15 these two, these are made with exactly the same
16 ingredients that I have shown, if you look at
17 that stability data, for the 110177, you get for
18 the two impurities values of .2 which is a total
19 of .4 over a six-month period.

20 If you look at the 110110 lot, you
21 getting values of less than .1.

22 Now, that's important because that's
23 illustrating the point. Even with the same
24 level, same -- using the same lots, we're getting

1 batch-to-batch variability of the components in
2 terms of their stability.

3 There is also another important
4 point to make here is that these values as shown
5 here actually come from a single patch. And if I
6 go to my next slide I'll show that point.

7 Only one patch is used to determine
8 degradation products. So you can see here it
9 talks about the impurities and the method test
10 one patch so here you have the data that's
11 generated for the stability data is simply from
12 one patch out of the thousands that are in that
13 particular batch.

14 In that case, I don't think you can
15 use the data from one patch. Together with my
16 concerns of the lot variability, you can't use
17 that information to draw conclusions about
18 whether acetaldehyde is acting to reduce the
19 oxidative degradation, or is an antioxidant in
20 Par's products.

21 MS. JACOBSEN: Your Honor, for the
22 record, Dr. Davies referred to PTX 348, page 778,
23 PTX 349 at page 786, and PTX 350 at page 796.
24 And those are the excerpts from Par's ANDA

1 specifications. And I'm told I misspoke. The
2 reference to PTX 350 was page 794. Dr. Davies
3 also referred to the stability data.

4 BY MS. JACOBSEN:

5 Q. And Dr. Davies, if you can turn to tab 25
6 in your witness book, can you identify that
7 document?

8 A. Yes, this is a portion of 3M's documents,
9 again, part of their ANDA highlighting stability.

10 Q. Was that the data that you relied on in
11 preparing the slide on patch-to-patch
12 variability?

13 A. That's correct.

14 MS. JACOBSEN: Your Honor,
15 plaintiffs move to introduce into evidence JTX
16 200.

17 MR. BROWN: No objection.

18 THE COURT: Admitted without
19 objection.

20 MS. JACOBSEN: For the record,
21 Dr. Davies referred to JTX 200 at pages 3M 9355
22 and 3M 9357.

23 BY MS. JACOBSEN:

24 Q. Dr. Davies, let's move to the second

1 issue, whether Par's ANDA describes products that
2 contain about .01 to about 0.5 percent by weight
3 of an antioxidant.

4 Can you explain the dispute with
5 respect to this claim element?

6 A. Yes. The dispute is whether or not the
7 acetaldehyde that's present in Par's product
8 falls within that claimed range.

9 Q. And does it?

10 A. It does based on the specification that
11 Par sets for acetaldehyde, the specification
12 states that there could be up to a thousand parts
13 per million which is .1 percent by weight.

14 Q. Did you compare the amount in Par's
15 specification with the '031 patent?

16 A. Yes, I did.

17 As I said, Paris shown on the left on
18 this slide, Par's own specification permits
19 not more than a thousand parts per million or 0.1
20 percent by weight of acetaldehyde. If you think,
21 that falls within the range of the '031 patent
22 claim of about 0.01 to about 0.5 percent by
23 weight of an antioxidant.

24 Q. What amounts that are permitted by Par's

1 ANDA specification fall within the claim range of
2 about 0.01 to about 0.5 percent by weight?

3 A. That would fall -- that would be from a
4 hundred to a thousand parts per million.

5 Q. And what's that in weight percent?

6 A. That is 0.01 to 0.1 percent by weight.

7 MS. JACOBSEN: For the record,
8 Dr. Davies referred to JTX 1, that's the '031
9 patent, and PTX 348, page 780, 349 and 788, 350,
10 and 796?

11 Q. And Dr. Davies, in providing your answer
12 of what amounts within Par's ANDA specification
13 fall within the claim range, were you also
14 considering in that answer the claim, scope of
15 the claim term about, or was that leaving that
16 aside?

17 A. Leaving that aside.

18 Q. And on Par's ANDA specification submitted
19 to the FDA?

20 A. Yes, they were.

21 Q. What was the basis for Par's ANDA
22 specification for acetaldehyde?

23 A. The basis was a scientific evaluation of
24 the acetaldehyde and also measurements of the

1 levels in prototype batches and what amount of
2 acetaldehyde were observed in Par's prototypes.

3 As this slide shows, in the
4 prototype patches they measured up to 402 parts
5 per million for one patch, and 224 parts per
6 million for others. That's 0.04 and 0.02 percent
7 by weight.

8 Q. And Dr. Davies, could you please turn to
9 tab 26 in your witness binder where you'll find
10 JTX 65?

11 A. Yes.

12 Q. Can you identify that document?

13 A. Yes, this is the document from which the
14 table is drawn.

15 MS. JACOBSEN: Your Honor,
16 plaintiffs move to introduce into evidence JTX
17 65.

18 MR. BROWN: No objection.

19 THE COURT: All right. Admitted
20 without objection.

21 MS. JACOBSEN: For the record,
22 Dr. Davies referred to JTX 65 at page 721.

23 BY MS. JACOBSEN:

24 Q. Dr. Davies, earlier you mentioned that 3M

1 detected the presence of acetaldehyde in Par's
2 ANDA products. What did they report?

3 A. Yes. This is a slide that I prepared to
4 show the acetaldehyde content in Par's
5 representative ANDA batches. I'm showing it for
6 the three dosing strengths. Two of the batches
7 they had levels that were not detected. The
8 remainder, six batches show levels ranging from
9 eight through to 30 parts per million of
10 acetaldehyde.

11 Q. And if Par gains FDA approval, is 300 --
12 sorry, is 30 parts per million the maximum amount
13 of acetaldehyde that Par's ANDA products are
14 permitted to contain?

15 A. No. If they gain FDA approval, they would
16 be able to manufacture batches up to a thousand
17 parts per million. That is up to .1 percent by
18 weight.

19 MS. JACOBSEN: And Your Honor, for
20 the record, Dr. Davies referred to JTX 180, 181,
21 196, 197, 198, 199, and PTX 352 and 353. And
22 Your Honor, we move to introduce those exhibits
23 into evidence.

24 MR. BROWN: No objection, Your

1 Honor.

2 THE COURT: All right. So those
3 eight exhibits are admitted without objection.

4 BY MS. JACOBSEN:

5 Q. Dr. Davies, can you summarize your
6 opinions relating to whether Par's ANDA products
7 meet the disputed elements of Claim 7?

8 A. I believe I have shown through my analysis
9 of my tests that Par's ANDA products contain an
10 antioxidant acetaldehyde, and I believe that
11 acetaldehyde in Par's ANDA product is present
12 within the claimed ranges of 0.01 to about 0.5
13 percent by weight.

14 Q. Thank you.

15 Dr. Davies, I would like to turn now
16 to the claim elements that are not in serious
17 disputed.

18 MS. JACOBSEN: Unfortunately we
19 stipulate that Par stipulated to infringement as
20 Your Honor requested that the parties meet and we
21 weren't able to reach an agreement so we'll make
22 this as quick as possible.

23 THE COURT: All right.

24 BY MS. JACOBSEN:

1 Q. So starting with the first claim element,
2 a transdermal device, under the parties' agreed
3 upon construction, are Par's ANDA products
4 transdermal devices?

5 A. Yes. It's a medical device for systemic
6 drug administration through intact skin. Par's
7 product clearly is a transdermal device, a device
8 that's meant to be applied to the skin with a
9 systemic drug administration through the skin.

10 Q. Can you turn to tab 27, PTX 343. Do you
11 recognize that document?

12 A. Yes. It's the patient prescribing
13 information that shows at the top there, a
14 transdermal system.

15 MS. JACOBSEN: Your Honor plaintiffs
16 move to introduce into evidence PTX 343.

17 MR. BROWN: No objection.

18 THE COURT: Admitted without
19 objection.

20 BY MS. JACOBSEN:

21 Q. And then the next claim element is a
22 pharmaceutical composition and do Par ANDA
23 products contain a pharmaceutical composition
24 under the agreed upon construction of that term?

1 A. Yes, it is, it's a composition suitable
2 for pharmaceutical use. Par represents that it
3 submitted to the FDA ANDA information which, it's
4 about a product that's suitable for
5 pharmaceutical use, for the treatment of
6 patients.

7 Q. And then the next element, therapeutically
8 effective amount of rivastigmine, is one of those
9 present in Par's ANDA products?

10 A. Yes. It's an amount sufficient to produce
11 the desired therapeutic effect. Par has
12 represented to the FDA that the dose is suitable
13 for treatment of dementia, Alzheimer and
14 associated with Parkinson's disease, of those
15 three dosage strengths.

16 Q. The next element is a diluent or carrier.
17 Do Parties' ANDA products contain a diluent or
18 carrier under the Par's agreed upon construction?
19

20 A. Yes. The inactive ingredient aids in the
21 administration of the drug. It contains an
22 adhesive. The adhesive is highlighted in the
23 patent as a diluent or carrier.

24 Q. And how does the adhesive aid in the

1 administration of Rivastigmine in Par's ANDA
2 products?

3 A. It aids in the administration because the
4 drug is contained within the adhesive and the
5 drug is released from the adhesive into the skin
6 and for systemic circulation.

7 Q. And then the last element is: Did Par's
8 ANDA products meet the limitation: Wherein the
9 pharmaceutical composition is supported by a
10 substrate?

11 A. That is supported structurally. The
12 pharmaceutic backing layer providing structural
13 support for the pharmaceutical. Par's patch has a
14 backing layer.

15 Q. And does that backing layer provide
16 structural support?

17 A. It does.

18 MS. JACOBSEN: Thank you, Dr.
19 Davies. We have no more questions at this time.

20 THE COURT: All right. Thank you.

21 Mr. Brown.

22 MR. BROWN: We have some binders and
23 things to hand up, Your Honor.

24 THE COURT: Surely.

1 MR. FINEMAN: Your Honor, permission
2 to approach?

3 THE COURT: Sure.

4 MR. BROWN: Permission to approach
5 the witness, Your Honor?

6 THE COURT: Sure. Yes.

7 CROSS-EXAMINATION

8 BY MR. BROWN:

9 Q. Good morning, Dr. Davies.

10 A. Good morning to you.

11 Q. I'm Dan Brown. We met at your deposition.

12 I'm representing Par. I have a few
13 questions to ask you today regarding your
14 testimony on direct.

15 You just testified on direct
16 examination that part of your basis for
17 concluding that acetaldehyde is an antioxidant is
18 that it is, in your words, a known reducing
19 agent; correct?

20 A. That's correct.

21 Q. And I'd like to turn to Exhibit JTX 060.

22 It's one of the binders that we provided to you.

23 Doctor, it's one that has JTX
24 exhibits in it. Can you find JTX 060?

1 And this is the Van Nostrand
2 dictionary that you cited in support of your
3 assertion that acetaldehyde is a known reducing
4 agent. And can we have that entry blown up on
5 the screen, please?

6 A. I don't seem to have it.

7 MR. KALLAS: We don't have it,
8 either.

9 BY MR. BROWN:

10 Q. In that case, I'll just go to -- can I
11 have Davies' Slide 8 up?

12 And this is a slide that you used on
13 direct examination for JTX 061, which is Van
14 Nostrand's Concise Encyclopedia of Science.

15 And am I correct that Van Nostrand's
16 Concise Encyclopedia of Science, despite
17 referring to acetaldehyde as a reducing agent,
18 never uses the term antioxidant to refer to
19 acetaldehyde?

20 A. That's correct.

21 Q. And if you could also turn in your
22 original binder that you used on direct
23 examination to Tab 10, which is JTX 063.

24 And I'd like to have actually

1 Davies' Slide 12 up. And that is the Specialty
2 Chemicals Sourcebook that you relied on on direct
3 examination; correct?

4 A. That's correct.

5 Q. And despite limited -- despite enumerating
6 a variety of possible uses for acetaldehyde here,
7 the Specialty Chemicals Sourcebook does not
8 identify acetaldehyde as an antioxidant; correct?

9 A. That's correct.

10 Q. And, Dr. Davies, if I see a particular
11 chemical compound referred to in the literature
12 as a reducing agent, isn't it correct that you
13 have no opinion as to whether that means it's an
14 antioxidant?

15 A. I believe -- I think I've said in my
16 depositions, it can be an antioxidant. Correct.

17 Q. Well, Dr. Davies, without conducting an
18 experiment on a reducing agent, you don't know
19 whether it's an antioxidant or a prooxidant;
20 correct?

21 A. I'm not sure that's correct.

22 Q. Well, you don't have an opinion, one way
23 or the other; correct?

24 A. Well, for acetaldehyde, I certainly do.

1 Acetaldehyde is a reducing agent, a known
2 reducing agent. And I've shown that it is an
3 antioxidant.

4 Q. My question is more general. It relates
5 to the relationship between reducing agents and
6 antioxidants. And if I see a compound referred
7 to in the literature as a reducing agent, without
8 conducting an experiment, you don't have an
9 opinion, one way or the other, about whether that
10 compound going to be an antioxidant or a
11 prooxidant; correct?

12 A. I think, as I've said, reducing agents can
13 be antioxidants, as I've said it at my
14 deposition.

15 Q. Can they also be prooxidants?

16 A. I don't think so, in the context of the
17 work that I've undertaken here. No.

18 Q. Well, Doctor, could you find your
19 deposition transcript in front of you? You
20 recall when I took your deposition in this matter
21 and I'd like you to find the June 5th version of
22 your deposition transcript and go to Page 177.

23 A. Thank you.

24 Q. And I'm reading from Page 177, Lines 5 to

1 19. And the question: "So, before you conduct
2 -- let me start over. Before you conduct any
3 experiment on a reducing agent, can you determine
4 whether it is an antioxidant or a prooxidant?

5 "Answer: Again, I have not been
6 asked to consider that in the context of what I
7 did. You're talking very generally there. But
8 in the context of what I did, acetaldehyde, a
9 known reducing agent, which is subject to
10 oxidation-reducing agents known to be
11 antioxidants in the context of my experiment, I
12 had every expectation that acetaldehyde would act
13 as an antioxidant and I've shown that."

16 A. That's correct.

17 Q. And while you have provided an opinion
18 that acetaldehyde is a known reducing agent, you
19 also have no opinion about whether it is a known
20 oxidizing agent; correct?

21 A. Well, it depends what you mean by opinion.
22 In the context of the work I've done, I believe
23 it's a reducing agent.

24 Q. But you don't have an opinion about

1 whether it's also a known oxidizing agent;
2 correct?

3 A. You mean as a prooxidant; I don't believe
4 it is in the context of the work.

5 Q. Well, if you can turn ahead in your June
6 5th deposition transcript to Page 180.

7 And I'm reading from Page 180, Line
8 14.

9 "Question: Are there different
10 conditions under which acetaldehyde is a known
11 oxidizing agent that is subject to being reduced?

12 "Answer: Again, you know, I've not
13 been asked to consider that. I have been asked
14 to consider the conditions, the kind of
15 conditions that the stress test, which
16 demonstrates the acetaldehyde, a known reducing
17 agent acts as an antioxidant that is susceptible
18 to oxidization and that is able to inhibit the
19 degradation of Rivastigmine in an oxidizing
20 environment."

21 So as of the day of your deposition,
22 you did not have an opinion about whether
23 acetaldehyde is also a known oxidizing agent;
24 correct?

1 A. I wasn't asked to consider that. That's
2 correct.

3 MS. JACOBSEN: Sorry. I object.

4 That was an incomplete -- the
5 previous question and answer of Dr. Davies'
6 deposition was specifically on this topic, and he
7 gave complete answers. And the two questions --
8 and Mr. Brown didn't show the Court those.

9 THE COURT: I'm sorry. Your
10 objection is?

11 MS. JACOBSEN: That was an
12 incomplete part of the deposition testimony. The
13 previous question and answer addresses this
14 issue.

15 THE COURT: All right. Well, on --
16 actually why don't we take care of this now. Can
17 you ask him about the previous question and
18 answer?

19 MR. BROWN: Certainly, Your Honor.

20 MS. JACOBSEN: Page 80, Lines 5 to
21 13.

22 BY MR. BROWN:

23 Q. And from Page 180, Lines 5 to 13.

24 "Question: Is acetaldehyde also a

1 known oxidizing agent that is subject to being
2 reduced?

3 "Answer: Acetaldehyde is a known
4 reducing agent that is susceptible to oxidation
5 in the context of the work that we're doing here
6 in the context of this experiment. I have shown
7 that and proven it -- that it acts as an
8 antioxidant in the context of the work of my
9 experiments."

10 THE COURT: All right. For what
11 it's worth, I don't actually think that needed to
12 be read to be complete, but it also causes no
13 harm.

14 Go ahead, Mr. Brown.

15 BY MR. BROWN:

16 Q. I'd like you to turn to JTX 1, the '031
17 patent. Now, you studied this patent carefully
18 in forming your opinions in this case; am I
19 correct?

20 A. Correct.

21 Q. And I'd like to put up a section of the
22 patent. This is at Column 4, Lines 10 to 19.
23 And this is the section of the patent where they
24 list the particular antioxidants that they

1 describe. And I'd like to look at the first
2 compounds listed here as an antioxidant
3 tocopherol acetate.

4 You agree that tocopherol acetate is
5 an antioxidant; correct?

6 A. It's listed in the patent. Correct.

7 Q. But you don't have any opinion as to
8 whether it's a reducing agent; correct?

9 A. I don't believe it is an reducing agent.

10 Q. At the time of your deposition, you didn't
11 have an opinion, one way or the other; correct?

12 A. That's correct.

13 Q. And looking at this list of antioxidants,
14 I'd next like to focus on ascorbyl palmitate.

15 Ascorbyl palmitate being listed as an
16 antioxidant, you have no opinion whether ascorbyl
17 palmitate would increase the oxidative
18 degradation of acetaldehyde in a transdermal
19 patch, isn't that correct?

20 A. I do. It depends which patch you're
21 talking about.

22 Q. In any rivastigmine transdermal patch, do
23 you have an opinion one way or the other whether
24 adding ascorbyl palmitate could cause an increase

1 in oxidative degradation in that patch?

2 A. I have an opinion based on the reading of
3 the patent that ascorbyl palmitate will act as an
4 antioxidant to reduce oxidative degradation.

5 Q. Let's look at page 161 of your June 5th
6 deposition transcript. And I'm reading from page
7 161 line 15 to page 162 line nine.

8 "QUESTION: Is it possible for
9 ascorbyl palmitate to increase the oxidation of
10 an active ingredient in a particular
11 pharmaceutical formulation?

12 "ANSWER: Again, I have not been
13 asked to consider that. I have not considered
14 that. That's not what I was asked to do, but I
15 believe Dr. Klibanov has talked at length about
16 these things. Please tell me, give me an
17 example, show me.

18 "QUESTION: Well, is it possible
19 that ascorbyl palmitate even though it's listed
20 here as an antioxidant could increase the
21 oxidation of rivastigmine and a transdermal
22 patch.

23 "ANSWER: Again, I have not been
24 asked to give an opinion on that."

1 That was your answer; correct?

2 A. You read it correct, but what you said
3 summarized what I just said, you're asking me very
4 general questions. You're asking me about a
5 specific issue, but I go on to talk about if you
6 go read down page 162, the patent is teaching me,
7 the patent is teaching me that, so it's clear that
8 I'm relying on the patent to teach you that, and
9 the antioxidants that are listed in this list, you
10 are trying to steer me to some other issue, but I
11 didn't know what you were talking about.

12 Q. Dr. Davies, if you continue on to the next
13 page at the top, line three to ten:

14 "QUESTION: So based on that
15 teaching, if I put ascorbyl palmitate into a
16 formulation, is it possible that the ascorbyl
17 palmitate will increase the oxidation of
18 rivastigmine?

19 "ANSWER: Again, you have asked me
20 this before, and I say I have not been asked to
21 consider that."

22 Isn't that, in fact, the answer you
23 gave me?

24 A. Yes. And I also said it's a very really

1 vague question, doesn't make sense, based on the
2 teaching of the patent. I go on to say the
3 patent clearly teaches you that antioxidants can
4 have a positive effect on these two formulations.
5 That's what I say. And you go on to ask me that
6 question over and over again.

7 Q. Doctor, I would like now to go to DTX 526.
8 And this is Van Nostrand's Encyclopedia of
9 Chemistry. You're familiar with this reference;
10 correct?

11 Let me know when you find it. And I
12 want to blow up an entry that's on the bottom
13 second column and going to the first line of the
14 second page. Can you pull that up, Bill. And I
15 want to read this section into the record.

16 An antioxidant ties up the peroxy
17 radicals so that they are incapable of
18 propagating the reaction chain or to decompose
19 the hydroperoxides in such a manner that carbonyl
20 groups and additional free radicals are not
21 formed. The former, which are called
22 chain-breaking antioxidants, free-radical
23 scavengers, or inhibitors, are usually hindered
24 phenols or amines. The latter, called peroxide

1 decomposers, are generally sulfur compounds or
2 organophosphites.

3 I just have a few questions for you
4 about this discussion. Now, alpha-tocopherol is
5 a well-known antioxidant; correct?

6 A. I'm sorry.

7 Q. Alpha-tocopherol is a well-known
8 antioxidant; correct?

9 A. It's listed in the patent.

10 Q. That's one of the categories of
11 antioxidants Dr. Klibanov testified in the Watson
12 trial was a quintessential antioxidant; right?

13 A. I don't recall him saying that.

14 Q. Well, alpha-tocopherol is the only
15 antioxidant for which there is data provided in
16 the '031 patent; correct?

17 A. I believe that's correct, specific data,
18 but the patent talks about the range of
19 antioxidants.

20 Q. But the data all comes from
21 alpha-tocopherol; correct?

22 A. I believe that's correct.

23 Q. And isn't it correct that you have no
24 opinion about whether alpha-tocopherol is a

1 hindered phenyl or an amine?

2 A. I believe it is, yeah, based on my
3 definition, that's correct.

4 Q. And, in fact, you have no opinion about
5 whether alpha-tocopherol functions as an
6 antioxidant by working as a free radical
7 scavenger or by working as a peroxide decomposer;
8 isn't that correct?

9 A. Based on my deposition, I believe it is a
10 free radical scavenger.

11 Q. That's a opinion you didn't have at your
12 deposition that you have today?

13 A. That's correct, I was tired, correct.

14 Q. And, in fact, for the list of compounds in
15 the '031 patent that we looked at a few minutes
16 ago at column four, lines 11 to 19, going down
17 that list, you haven't formed an opinion as to
18 whether each one of those compounds would be a
19 hindered phenyl, an amine, a sulphur compound or
20 an organophosphites, isn't that correct?

21 A. I wasn't asked, correct.

22 Q. Dr. Davies, I would like to ask you some
23 questions about first about the experiment that
24 you conducted that you testified about on direct

1 examination, JTX 66. Can you find JTX 66,
2 Dr. Davies?

3 A. I don't have it.

4 MR. BROWN: Permission to approach.

5 THE COURT: Yes.

6 BY MR. BROWN:

7 Q. Dr. Davies, you agree that this type of
8 test that's reported here in JTX 66 can be
9 referred to as a forced degradation study?

10 A. Yes.

11 Q. And you also refer to it as a stress test;
12 correct?

13 A. Sorry, I apologize. It's known as a
14 forced degradation study as well as a stress test;
15 correct.

16 Q. And Dr. Davies, isn't it true that you are
17 not aware of a single instance in the published
18 literature where a forced degradation study was
19 used to evaluate whether a particular chemical
20 compound served as an antioxidant in a finished
21 pharmaceutical dosage form?

22 A. I disagree.

23 Q. Well, Dr. Davies, do you recall at your
24 deposition that I asked you several times to

1 identify any literature reference of which you
2 are aware in which a forced degradation study was
3 used to evaluate whether or not a particular
4 compound served as an antioxidant?

5 A. I do, and I replied at length. I replied
6 that I rely on the literature that I cited in my
7 reports. I talked about it at length.

8 Q. Do you recall that I asked you to prepare
9 a list for me of every published literature
10 reference of which you were aware that described
11 using a forced degradation study to evaluate
12 whether a compound was an antioxidant?

13 A. I do, indeed.

14 Q. And could you turn to DTX 105, which is
15 Davies 17.

16 Now, Dr. Davies, DTX 105 is, in
17 fact, a list you prepared for me at the
18 deposition of every literature reference of which
19 you are aware where a forced degradation study
20 was used to evaluate whether a compound was an
21 antioxidant; correct?

22 A. This is the sheet. As I told you at the
23 time, I provided a list of -- I provided many
24 references which I relied on in my reports. I

1 told you at the time and on a number of occasions
2 on a repeated questioning that I relied on those
3 papers from my reports.

4 MR. BROWN: Your Honor, Par would
5 move to admit DTX 105 into evidence.

6 MS. JACOBSEN: No objection.

7 THE COURT: Admitted without
8 objection.

9 BY MR. BROWN:

10 Q. Can you give me a citation right now,
11 Doctor?

12 A. I can give you examples that I described
13 in my reports and depositions, the example, the
14 example of the Alsante.

15 Q. Thank you, Doctor. We'll get to that in a
16 minute.

17 Now, I would like to look for a
18 minute at JTX 1, the '031 patent, at column four,
19 line 20 to 30. And now here, Doctor, am I
20 correct that the '031 patent describes conditions
21 for two stress tests?

22 A. I'm sorry, I didn't hear you.

23 Q. Am I correct that this section of the '031
24 patent, column four, lines 20 to 30, describes

1 two different sets of conditions for stress
2 tests; correct?

3 A. That's correct.

4 Q. One of those tests was conducted at three
5 months at 40 degrees C and 75 percent room
6 humidity; correct?

7 A. Correct.

8 Q. And the other test was run for two months
9 at 60 degrees C; correct?

10 A. Correct.

11 Q. And both of these tests were conducted on
12 quote, the pharmaceutical composition of the
13 present invention; correct?

14 A. That's correct.

15 Q. Now, I would like to refer now back to JTX
16 66. Your forced degradation study. You were the
17 person who designed this forced degradation study;
18 correct?

19 A. I was.

20 Q. And in addition to the forced degradation
21 study, you have done a total of two other tests
22 that you relied on over the course of this action
23 for your opinions regarding Par's ANDA products;
24 correct?

1 A. You mean the peroxide and the oxygen
2 level?

3 Q. That's exactly what I mean.

4 A. I see. Okay. Yes, correct.

5 Q. And the peroxide value test and the oxygen
6 saturation test, are those the two tests you're
7 referring to?

8 A. I believe so.

9 Q. And you designed and conducted the
10 peroxide value test and the oxygen saturation
11 test in February of 2013 in response to opinions
12 that Par's experts provided in the case; correct?

13 A. That's correct.

14 Q. And could you please turn to DTX 111. And
15 DTX 111 is the laboratory notebook work -- let me
16 restate the question.

17 DTX 111 is the laboratory notebook
18 that reports all of the work done in connection
19 with the peroxide value test and the oxygen
20 saturation tests that you conducted in February
21 of 2013; correct?

22 A. I believe that's the case.

23 MR. BROWN: Par would move to admit
24 DTX 111.

1 MS. JACOBSEN: No objection.

2 THE COURT: Admitted without
3 objection.

4 MS. JACOBSEN: No objection.

5 THE COURT: Admitted without
6 objection.

7 BY MR. BROWN:

8 Q. Now, if you could now turn to JTX 170 in
9 your binder.

10 Now, JTX 170 is the laboratory
11 notebook that records the laboratory work that
12 went into your forced degradation study that we
13 looked at at JTX 066; correct?

14 A. I'm sorry. I'm trying to find it.

15 That's correct.

16 Q. And the cover, the date on the cover of
17 this notebook tells you that it was generated on
18 October 29th, 2012; correct?

19 A. Correct.

20 Q. So I'm going to start a timeline that
21 we've put together and I want to put that date up
22 on the timeline.

23 MR. BROWN: So, Bill, can you put up
24 the timeline with that date showing?

1 BY MR. BROWN:

2 Q. Now, it didn't take you very long to
3 design the forced degradation study; correct?

4 A. In what sense? Once I decided to do that
5 test, correct. About a week.

6 Q. And in your opinions in this case
7 regarding the forced degradation study, JTX 066,
8 you were not relying on any testing that you or
9 anyone on your behalf conducted prior to
10 October 29th, 2012; correct?

11 A. No, I'm not.

12 Q. And when you designed the forced
13 degradation study, you expected that it would
14 take about a week or so; correct?

15 A. That's correct. When I made that decision
16 to do it, yes.

17 Q. And the process of conducting the
18 experimental testing for the forced degradation
19 study took about ten days running from October
20 29th to November 7th, 2012; correct?

21 A. Correct. That's running the experiment.
22 Then I had to analyze the data.

23 Q. So I want to add that November 7th date to
24 our timeline. Now, the Rivastigmine active

1 ingredient that you used in the forced
2 degradation study was shipped directly to you in
3 the United Kingdom from the 3M Company; correct?

4 A. That's correct.

5 Q. And if you could find JTX 33. JTX 33 is a
6 chain of custody document that you prepared in
7 this case; correct?

8 A. That's correct.

9 Q. And if you could turn to Page 4, there's a
10 section entitled Actavis' Rivastigmine sample.

11 Do you see that?

12 A. That's correct.

13 Q. And you understand that Par now owns the
14 ANDA that previously belonged to Actavis;
15 correct?

16 A. That's correct.

17 Q. And so this chain of custody document
18 demonstrates that you received the sample of
19 Rivastigmine active ingredient from 3M on
20 September 10th, 2012; correct?

21 A. That's correct.

22 Q. And I'd like to put that date onto the
23 timeline. And after you received the sample on
24 September 10th, you stored that sample at

1 Molecular Profiles until you used it beginning
2 around October 29th; correct?

3 A. That's correct.

4 Q. Now, in addition to the Rivastigmine
5 active ingredient that you received on
6 September 10th, you received a number of other
7 samples in this matter from 3M Corporation
8 relating to the Par product; correct?

9 A. That's correct.

10 Q. In fact, before you conducted any work in
11 this case, you requested a variety of samples
12 relating to the Par 3M patch; correct?

13 A. I believe that's correct.

14 Q. Could you please look at DTX 113 in the
15 binder in front of you?

16 DTX 113 is an April 20th, 2012
17 letter from Novartis' counsel, Chris Loh;
18 correct?

19 A. That's correct.

20 Q. And now I'd also like you to turn to DTX
21 120. This is a document Entitled Plaintiffs'
22 Third Set of Requests to Actavis for the
23 Production of Documents and Things. And it's
24 dated May 1st, 2012.

1 I'm going to come back to DTX 113
2 and 120 in a second. I'd like to go now to DTX
3 112.

4 Now, this is a letter dated June 1,
5 2012 from Novartis' counsel, Chris Loh. And I'd
6 like to blow up the first sentence in the second
7 paragraph of DTX. The first sentence in the
8 second paragraph, please.

9 And there it says, As I mentioned
10 during that call, our April 20, 2012 and May 1,
11 2012 requests for samples of Actavis' ANDA
12 products and the active ingredients, excipients
13 and materials used therein were determined in
14 consultation with our expert.

15 And now I want to blow up -- if we
16 can leave that on there, I want to blow up the
17 rest of it. The following paragraph continues:
18 "To clarify matters, our expert, Martyn Davies,
19 believes that the requested sample quantities are
20 reasonable and necessary in view of three
21 enumerated items; correct?

22 A. That's correct. That's what it says.

23 Q. And number three is the number of tests he
24 has in mind; correct?

1 A. Correct.

2 Q. And, in fact, you believed, based on your
3 experience in undertaking work on pharmaceutical
4 formulations, that you required the sample
5 quantities referenced in the April 20th and May
6 1st requests shown in DTX 113 and DTX 120?

7 A. That's correct. Because I didn't know
8 what experiments I would be doing, so I wanted to
9 have sufficient numbers so I could do the
10 experiments if they were required.

11 Q. Dr. Davies, your research and work at
12 Molecular Profiles relates to the development and
13 characterization of pharmaceutical dosage forms
14 in drugs; correct?

15 A. That's correct.

16 Q. And isn't it true that in view of your
17 experience in undertaking work on pharmaceutical
18 formulations, you thought that the samples
19 identified in DTX 113 and DTX 120 were reasonable
20 and necessary?

21 A. Oh, absolutely, of that type. When I
22 was -- before so I'd have sufficient samples, so
23 if I wanted to do some experiments.

24 Q. Well, let's look back at DTX 113 and see

1 what you thought were reasonable and necessary,
2 and if I can blow up the list provided there.

3 It included 200 patches of the 4.6
4 milligram product. Another 200 patches of the
5 9.5 milligram product. 200 empty pouches.

6 Five square meters of the 3M
7 Scotchpak laminate backing. Five square meters
8 of Scotchpak release liner.

9 Another five square meters of the 3M
10 Scotchpak in process release liner. One kilogram
11 of the 3M R-27149 solvated acrylate copolymer
12 adhesive.

13 One kilogram is about 2.2 pounds;
14 correct?

15 A. I have no idea what it is in pounds.

16 Q. And a hundred grams of the Cognis
17 isopropyl myristate tackifier. Ten grams of the
18 Rivastigmine API and one five-gallon core carboy.

19 Those are the materials that you
20 thought were reasonable and necessary in this
21 case; correct?

22 A. That's correct.

23 Q. Now, could you please turn to DTX 114?

24 Now, this is a letter dated August

1 3, 2012 from 3M to yourself at your address at
2 Molecular Profiles in the U.K.; correct?

3 A. That's correct.

4 Q. And 3M sent you by FedEx the samples you
5 requested; isn't that correct?

6 A. I believe that's correct. They were
7 requested by counsel. That's correct.

8 Q. And you, in fact, received the items
9 listed here, one to ten in this letter?

10 A. That's correct.

11 Q. And after you received the ten enumerated
12 items here from 3M, you put them in your store
13 room at Molecular Profiles; correct?

14 A. I did.

15 Q. And do you see at the top of this letter,
16 DTX 114, that 3M designated the materials that it
17 gave you Highly Confidential Outside Counsel
18 Only?

19 A. Yes.

20 Q. And you, in fact, honored that
21 designation; correct?

22 A. Yes.

23 Q. And from the time you received the samples
24 in August 2012 until February 2013, when your

1 experiments in this case were complete, none of
2 the samples that 3M shipped to you ever left the
3 premises of Molecular Profiles; correct?

4 A. That's my understanding. Correct.

5 Q. Now, turning to the second page of DTX 114
6 at the very end, it states that 3M is not
7 enclosing the requested Rivastigmine active
8 ingredient samples.

9 Do you see that?

10 A. I do.

11 Q. And you received those as we looked at a
12 minute ago on September 10th; correct?

13 A. That's correct.

14 Q. So I'd like to add this August 3rd
15 shipment to the time line.

16 Now, Doctor, isn't it correct that
17 in the forced degradation study that you relied
18 on for your infringement positions in this case
19 you, in fact, used none of the materials that
20 were shipped to you with the August 3rd, 2012 3M
21 shipment?

22 A. That's correct.

23 Q. And am I correct that at no time between
24 August 3rd, 2012 and October 29th, 2012 were you

1 in the process of conducting any experiments that
2 you are relying on in this case for your opinions
3 regarding the Par ANDA Rivastigmine patch?

4 A. That's correct.

5 Q. I'd like you to turn in your binder to DTX
6 568. This document is entitled Plaintiffs'
7 Second Supplemental Responses to Actavis'
8 Interrogatories Number 1 and 2.

9 And I'd like you to first turn to
10 Page 15 of this document. And do you see the
11 document is dated August 23rd, 2012?

12 A. I do.

13 Q. And this is before you received the active
14 ingredient Rivastigmine from 3M; correct?

15 A. That's correct.

16 Q. And I'd like you to turn back to Page 11.
17 And do you see at Page 11 purports a claim chart
18 with the '031 patent claim elements in the first
19 column, and in the second column it states how
20 claim elements are met by the Actavis' ANDA
21 product, which is now the Par ANDA product;
22 correct?

23 A. I see that.

24 Q. And I'd like to blow up Element B all the

1 way through to the second column.

2 And under Element B, the
3 interrogatory response states, "Plaintiffs are in
4 the process of testing Actavis' ANDA products to
5 identify and quantify the antioxidant(s) expect
6 such testing to be complete in two to
7 two-and-one-half months, and will provide
8 supplemental responses at that time or earlier,
9 if the testing is completed sooner than expected.

10 So I have some questions for you
11 about this statement. Now, as of the August 23rd
12 date of this response, none of the testing that
13 you have disclosed and relied on in this
14 litigation regarding the Par ANDA product was in
15 the process of being conducted; correct?

16 A. That's correct.

17 Q. Regarding the Par ANDA products was in the
18 process of being conducted; correct?

19 A. That's correct.

20 Q. So the testing of Actavis' ANDA products
21 to identify and identify the antioxidant
22 referenced in this response does not refer to any
23 of the testing that you referred to in this case;
24 correct?

1 A. Correct. I don't know what this refers
2 to.

3 Q. I would like to focus on the next
4 statement that plaintiffs quote, expect such
5 testing to be complete in two to two-and-a-half
6 months.

7 I would like to go back to the
8 timeline. And you will agree with me, will you
9 not, the very beginning of the first experiment
10 you were relying on in this litigation,
11 specifically the October 29th date of your
12 laboratory notebook occurred two to
13 two-and-a-half months after the August 23rd date
14 of this interrogatory response?

15 A. I accept that.

16 Q. Well, I would like to see if we can shed a
17 little more light about what might have been
18 referred to in this interrogatory response since
19 you said you don't seem to know.

20 MR. BROWN: Permission to approach.

21 THE COURT: Sure.

22 BY MR. BROWN:

23 Q. Now, what I have handed you, Doctor, is a
24 transcript of a discovery proceeding that

1 occurred in this court. This is DI-77 in this
2 action. It occurred on July 1st, 2012. And I
3 want to put up a section of the discovery
4 proceeding that runs from page 13 line 19 to page
5 14 line 9. And in this section of the
6 transcript, Novartis' counsel, Mr. Prugo, is
7 telling the Court that Novartis needs extra time
8 for discovery in the case because of the testing
9 of the ANDA products will take about three
10 months.

11 And, in fact, he says, The testing
12 will take about three months. And there are the
13 three months that are talked about in this
14 specification, so the whole point here is that
15 you have to have a stable active ingredient, and
16 the accelerated stability testing described in
17 the specification is three months long.

18 So, Doctor, I want to ask you about
19 that statement. Isn't it true that as of August
20 23rd, 2012, you believe that the correct test for
21 antioxidant behavior was the three-month
22 stability testing described in the '031 patent
23 specification?

24 A. No. But I didn't say this, this is

1 somebody else's words, not mine.

2 Q. Isn't it a fact, Doctor, that you designed
3 and conducted your forced degradation study only
4 after you knew the results of whatever testing is
5 described in the August 23rd interrogatory
6 response?

7 A. No. I designed my testing as I described
8 in my direct, because I couldn't do that
9 head-to-head study.

10 Q. Doctor, did you or did you not know the
11 results of the testing that's being described in
12 the August 23rd, 2012 discovery response when you
13 designed your October 29th test?

14 A. No. Sorry, you mean at this time, in this
15 -- how could I?

16 Q. My question relates to the time that you
17 designed your October 29 test, and my question
18 for you is: Did you or did you not know the
19 results of the testing that's described in the
20 August 23rd, 2012 discovery response when you
21 designed your test?

22 A. I don't know what that test is. This is
23 somebody else's words, not my test.

24 Q. Doctor, since you were the only person

1 that had Actavis' ANDA products that had been
2 shipped to plaintiffs, who else could have been
3 doing that test?

4 A. I have no idea. I don't know what this is
5 related to. It's nothing to do with me, it has
6 to do with the lawyers.

7 Q. Now, Doctor, on direct examination, you
8 said you did not see enough degradation at 40
9 degrees C or room temperature to do the forced
10 degradation experiment on the time schedule you
11 had in mind; correct?

12 A. That's correct.

13 Q. And your opening expert reports in this
14 case were due November 19th, 2012; correct?

15 A. That's correct.

16 Q. And so isn't the lack of time that you're
17 complaining about something that happened because
18 we don't have any evidence of what you were doing
19 before October 29th, 2012 with all of these
20 materials?

21 A. No. It's purely come down to the design
22 of the experiment. Over the time scale I wanted
23 to study the experiment, that's why I chose 60
24 degrees, again, faster.

1 Q. So it only took you a week to design it;
2 right?

3 A. That's about right.

4 Q. And it took you about another week to do
5 it?

6 A. Correct.

7 Q. So if you started it back in September
8 when you got the active ingredient, you would
9 have had months and months to look for the
10 results; correct?

11 A. But then as you know, I was doing lots of
12 things at that time. I was also doing the work
13 for the other; art -- what was the other part
14 of the case, the Watson case. I also had my
15 other work to do, my university work and the
16 like. So I designed that test and I did that
17 test I think in an appropriate manner.

18 Q. So, Doctor, you're telling us that the
19 reason you didn't start your test until October
20 29th, 2012 is because of the testing you were
21 doing in the Watson case and other work at the
22 university and not because you were awaiting
23 results of a different test?

24 A. Correct. Due to the fact that I was doing

1 multiple things at that time, and I was -- made
2 the decision to run that specific test based on
3 what I saw in the ANDA, what I saw in the -- for
4 the information that I had related to the
5 products, and I decided to run that test.

6 Q. I would like to go to your -- I would like
7 to switch topics now, Doctor, and go to your
8 slide 26.

9 THE COURT: Mr. Brown, if you're
10 switching topics, would this be a good time to
11 break for lunch?

12 MR. BROWN: It would be perfect.
13 Thank you, Your Honor.

14 THE COURT: So we'll take an
15 approximately one-hour recess. And, Dr. Davies,
16 you can't talk with your lawyers during this
17 break. And do you have these resumes that I want
18 to look at?

19 MR. FINEMAN: Yes.

20 MR. BROWN: Your Honor, we have the
21 CV's for two of our experts, the third one won't
22 be testifying until tomorrow.

23 THE COURT: That will be fine. All
24 right. Thanks. We'll be in recess. See you

1 again at quarter to 2:00.

2 (A brief recess was taken.)

3 THE CLERK: All rise.

4 THE COURT: All right. Good
5 afternoon, everybody. Be seated, please.

6 Are we ready to continue, Mr. Brown?

7 MR. BROWN: Yes. And, Your Honor,
8 during the examination before lunch, there were a
9 few exhibits that I had neglected to move for
10 admission.

11 I'd like to go ahead and move for
12 admission of JTX 33, DTX 112, 113, 114, 120, 526
13 and 568.

14 MS. JACOBSEN: No objection.

15 THE COURT: All right. They're all
16 admitted without objection.

17 BY MR. BROWN:

18 Q. Good afternoon, Dr. Davies.

19 A. Good afternoon.

20 Q. Could I have Slide 26 up from the direct
21 examination?

22 Now, I want to ask you just a couple
23 questions about the stock solution that's
24 referenced there in the left-hand column. And

1 the Rivastigmine concentration that you have
2 there is approximately .36 percent; correct?

3 A. That's correct.

4 Q. And in your stock solution, you have 1.3
5 percent approximately of T-butyl hydroperoxide;
6 correct?

7 A. That's correct.

8 Q. And that's roughly three times as much of
9 the peroxide as there is of the active ingredient
10 Rivastigmine; correct?

11 A. Correct.

12 Q. And you would agree that in a normal
13 pharmaceutical product, you're not likely to
14 encounter three times as many peroxides as the
15 active ingredients?

16 A. I am not sure of that. Well, of course,
17 there would be less peroxides, of course.

18 Q. Now, Doctor, in your forced degradation
19 study, you didn't test any known antioxidant such
20 as alpha tocopherol using the same experimental
21 protocol to see if it would prove effective under
22 the conditions of your experiments; correct?

23 A. That's correct. I didn't need to.

24 Q. And, in fact, you didn't test any of the

1 compounds listed in Column 4, Lines 11 to 19 to
2 see if your test would demonstrate an antioxidant
3 effect for those known antioxidant compounds;
4 correct?

5 A. That's correct.

6 Q. Can I have up Davies' Slide 22?

7 And I believe you testified on
8 direct that for all of the vials that you have
9 here, C1 C2, C3, A1, A2 and A3, you never
10 measured the amounts of acetaldehyde in any of
11 those vials at any of the time points in your
12 study; correct?

13 A. That's correct.

14 Q. And you never did a control experiment
15 where you measured the amount of acetaldehyde in
16 a vial stored at 60 degrees C over 21 hours to
17 see what happens to the acetaldehyde under those
18 conditions?

19 A. Well, I did a control. I did do that
20 experiment.

21 Q. And in your experiment, you also did not
22 measure the oxygen content of any of the six
23 vials that you were measuring; correct?

24 A. That's correct.

1 Q. And, Doctor, are you aware that the
2 reaction of acetaldehyde with oxygen or air
3 produces peroxides?

4 A. I am aware. It can produce peroxides.

5 Correct.

6 Q. Now, in this litigation, you did
7 measure -- you did conduct an oxygen saturation
8 measurement on Par's ANDA product to see if there
9 was oxygen there; correct?

10 A. That's correct.

11 Q. And you provided the opinion that Par's
12 product does, in fact, have oxygen in it;
13 correct?

14 A. That's correct.

15 Q. Now, I'd like to look at one of your
16 experiments in particular and can you find JT^X
17 066 in the binder?

18 A. I've got it.

19 Q. And I'd like to look at Pages 8 and 9.
20 Can we go forward to that?

21 And I'd like to focus particularly
22 on Sample A3 at the 15-hour time point and sample
23 A3 at the 21-hour time point.

24 And so, in looking at these data,

1 the middle value there is the value for
2 Rivastigmine and I want to ask you about that.

3 So, at the 15-hour time point, the
4 raw area value you measured for Rivastigmine was
5 6,937 units; correct?

6 A. Correct.

7 Q. And at the 21-hour time period time point,
8 the raw area of Rivastigmine that you measured
9 was 10,185 area units; correct?

10 A. That's correct.

11 Q. And so the raw area for the Rivastigmine
12 peak actually increased by approximately 50
13 percent in the experiment; correct?

14 A. That particular volume, that's correct.

15 But, of course, I explained that in the context
16 of this work, that all the other peaks increased
17 pro rata. And I say that for that A3 sample, the
18 21 hours that I believe the top of the vial may
19 have been not sealed properly in the HPLC system,
20 so we may have lost some solvent.

21 Q. Because it's not possible that the amount
22 of Rivastigmine would increase in that time
23 period; correct?

24 A. That's correct.

1 Q. And --

2 A. That's why all the degradants relative to
3 each other stay the same.

4 Q. And the conclusion you drew upon looking
5 at the data was that it is possible that this
6 increase in the raw data was due to evaporation
7 of a portion of the solvent in that vial upon
8 loosening of the seal for that vial; correct?

9 A. That's correct.

10 Q. Now, if you could turn to JTX 170, that's
11 the laboratory notebook for this experiment.
12 There is no reference to any loosened seal or
13 evaporated solvent recorded in the lab notebook
14 for this experiment; correct?

15 A. There is a record that we subsequently
16 re-analyzed that Sample three times just to
17 double-check.

18 Q. Understood. But no one wrote down that
19 the seal was loose and the solvent evaporated;
20 correct?

21 A. I would have to check it, but I don't have
22 it in front of me.

23 Q. 170 is in the Davies cross exhibit binders
24 of JTX and PTX exhibits. Can you confirm that

1 for me?

2 A. That's correct, it just says it's done in
3 triplicate.

4 Q. So now at the various time points of your
5 experiment including the end, you also didn't
6 measure the amount of solution that was left in
7 each vial; correct?

8 A. That's correct, I didn't need to.

9 Q. And so there is no way of knowing if any
10 of the other seals also allowed some of the
11 solvent to evaporate; correct?

12 A. No. That's incorrect. Consistency of the
13 data shows as I explained in my reports, shows
14 that they were sealed.

15 Q. Doctor, you were not physically present in
16 the lab the day the vials were placed in the oven
17 and the day the measurements were taken; correct?

18 A. That's correct.

19 Q. Acetaldehyde boils at around 20 degrees
20 Celsius; correct?

21 A. Pure acetaldehyde does, correct.

22 Q. And in your experiment at 60 degrees C,
23 you were 40 degrees above acetaldehyde's boiling
24 point; correct?

1 A. Correct, the boiling point of pure
2 acetaldehyde.

3 Q. So if we assume that your supposition that
4 the result in the A3 vial was caused by solvent
5 evaporation, do you know if all the solvent had
6 evaporated out when the seal broke -- sorry. Do
7 you know if all of the acetaldehyde had
8 evaporated out when the seal broke?

9 A. No, because if you look at the data, you
10 look at the data relative to degradation relative
11 to the drug on that particular sample, it's the
12 same relative ratios that you see in the other
13 two vials for that time point, so, no.

14 Q. So you're inferring the presence of
15 acetaldehyde from your results; correct?

16 A. I know it's there because we put it in
17 there, and it's in a sealed system. It's there.
18 The results show that.

19 Q. Thank you, Doctor.

20 I want to move on and ask you a
21 little -- a couple of questions about the
22 statistical discussion that you provided on
23 direct examination.

24 Doctor, you first provided the

1 results of your forced degradation study in your
2 opening expert report that was served on November
3 19, 2012; correct?

4 A. That's correct.

5 Q. At that time the only statistical analysis
6 you provided was a T-test using a one-tailed
7 distribution; correct?

8 A. That's correct, I felt that was
9 appropriate.

10 Q. And you subsequently provided the
11 statistical analysis using the two-sided T-test
12 and the linear regression model that you
13 discussed here; correct?

14 You didn't give an audible answer,
15 but I think you nodded your head yes?

16 A. Sorry, I can't hear you.

17 Q. I'm sorry. After the November 19th
18 report, at a subsequent time you provided the
19 statistical analysis using the two-sided T-test
20 and the linear regression model; correct?

21 A. That's correct, in response to
22 Dr. Michniak-Kohn's comments.

23 Q. And a one-tailed T-test is appropriate
24 only when the investigator has an a priori

1 expectation of the direction of the result;
2 correct?

3 A. I think that's correct. And I did have --
4 as I explained on direct, I did have that
5 expectation.

6 Q. And in this case you used the one-tailed
7 T-test rather than a two-tailed test because you
8 had an a priori expectation that acetaldehyde
9 would reduce the oxidative degradation of
10 rivastigmine rather than increase it; correct?

11 A. Not quite correct. I had the expectation
12 either it has no effect or it would reduce the
13 oxidative degradation, so it's in one direction.

14 Q. And you based your a priori expectation
15 that acetaldehyde would reduce or
16 have no effect on the degradation of rivastigmine
17 in part on your knowledge that acetaldehyde was a
18 known reducing agent; correct?

19 A. In part, correct.

20 Q. So a couple of questions about that.

21 Dr. Davies, you provided opinions in
22 the August trial against Watson about the
23 compound BHT; correct?

24 A. Correct.

1 Q. And BHT is a known antioxidant; correct?

2 A. Correct.

3 Q. And ascorbyl palmitate is another known
4 antioxidant; correct?

5 A. They are listed in the patent, that's
6 correct.

7 Q. And ascorbyl palmitate is one of the
8 antioxidants that you call a reducing agent;
9 right?

10 A. That's correct.

11 Q. Let's go to JTX 187. Can find that in the
12 binder?

13 MR. BROWN: We would move to admit
14 JTX 170 if it wasn't already admitted.

15 MS. JACOBSEN: No objection.

16 THE COURT: Admitted without
17 objection.

18 BY MR. BROWN:

19 Q. You have seen JTX 187 before; correct?

20 A. I'm not sure I have.

21 Q. Well, Doctor, JTX 187 is the
22 pharmaceutical development report prepared by one
23 of the plaintiffs here, LTS Lohmann, and I
24 believe you testified that a pharmaceutical

1 development report is a document that is often
2 included in an ANDA to give the regulatory
3 authority a general idea of how a formulation was
4 developed; correct?

5 A. That can be done, absolutely, I agree.

6 Q. I would like you to turn to page 504454.

7 I'm putting it up on the screen now. This page
8 shows the oxidative degradation pathway that you
9 testified about on direct examination; correct?

10 A. Correct.

11 Q. And the two oxidation impurities that you
12 measured in your forced degradation study are the
13 ones identified here as 802-95 and 213-95;
14 correct?

15 A. That's correct.

16 Q. 213-95 is the compound known as Impurity
17 4?

18 A. Correct.

19 Q. And 802-95, also called styrene, is the
20 compound known as ECAV; correct?

21 A. Correct.

22 Q. And I'd like to turn ahead in JTX 187 to
23 Page N504460.

24 And I want to blow up Table 5 from

1 this report on the screen, along with the text
2 immediately above the table. And in the text
3 above the table, it says two antioxidants
4 ascorbyl-palmitate and tocopherol have been added
5 as single substances in a concentration of 0.1
6 percent and in combination to formulation 2200.
7 The TDS have been packed in Barex-pouches and
8 stored at 60 degrees C for eight weeks.

9 In Table 5, the detected amounts of
10 the two main degradation products are listed.
11 And you understand TDS means transdermal system;
12 correct?

13 A. I believe that's the case.

14 Q. I'd like to look at what they found out
15 about ascorbyl-palmitate in this study. So I'd
16 first like to look at the first two lines of the
17 study, the formulation 2200 with no antioxidants
18 and the addition of .1 percent tocopherol.

19 Can you describe the effect that
20 adding .1 percent tocopherol had on formulation
21 2200?

22 A. Again, I -- well, I haven't been asked to
23 comment on this, but it appears to reduce the
24 level, the overall levels of the ketone or

1 styrene.

2 Q. In fact, it substantially reduces the
3 ketone and the styrene; correct?

4 A. Well, I agree it's reducing significantly.
5 Yeah.

6 Q. So now I'd like to compare the second
7 line. Excuse me.

8 Yeah. I'd like to compare the
9 second line with the fourth line. And the only
10 difference between those two formulations,
11 Doctor, is the addition of .1 percent
12 ascorbyl-palmitate; correct?

13 A. Actually, I don't -- well, that's what it
14 says here. I haven't read this document. So
15 that's what it says here.

16 Q. Well, let's look at the effect that they
17 observed in this experiment between those two
18 formulations. The amount of the 213-95 ketone
19 approximately doubled; correct?

20 A. It goes -- I agree.

21 Q. And the amount of ECAV 802-95 went from
22 .66 to 2.18 percent; correct?

23 A. That's correct.

24 Q. So it basically tripled?

1 A. Of that order.

2 Q. So, Doctor, if you had formed an a priori
3 expectation before this experiment that adding
4 ascorbyl-palmitate could only reduce rather than
5 increase the oxidation of Rivastigmine, you would
6 have been wrong; correct?

7 A. No, because if you look at the total
8 amount of the two key degradation amounts,
9 irrespective of the three examples shown, they're
10 much lower than the degradation products of the
11 2200.

12 So if you add up the degradation
13 products for the 2200, that's of the order of
14 five percent. Then if you add up the other
15 degradants, then it's much lower in each case.

16 Q. But, Doctor --

17 A. So I wouldn't make that assumption.

18 Q. But, Doctor --

19 A. Make the assumption -- three compounds are
20 all acting as antioxidants because they're
21 reducing the oxidative degradation to the
22 compounds.

23 I mean, I haven't read this in
24 detail, so you're just showing me a small portion

1 of this. But just as a scientist just sitting
2 here, you know, you've got three, three
3 antioxidants.

4 So, and they're all reducing the
5 level of oxidative degradation of the two
6 degradation products.

7 Q. Doctor, the only difference between the
8 second experiment and the fourth experiment is
9 the addition of the ascorbyl palmitate; correct?

10 A. I don't know that in detail, but I -- you
11 know, I can see it over here. Ascorbyl palmitate
12 is ascorbyl palmitate.

13 Q. I'd like you to turn to JTX 91.

14 And this is a document that you
15 cited in your surreply report in this case and
16 you've read this document; correct?

17 A. I have. That's correct.

18 Q. And this reference reports work done by
19 researchers at Pfizer to evaluate the effect of
20 an antioxidant BHT on their drug formulation;
21 correct?

22 A. Yes, on their coatings. That's correct.

23 Q. And I want to go to Page 123 of the
24 reference and I want to blow up a section where

1 they're reporting their conclusions.

2 Yes. And I'm highlighting a
3 sentence there where they reported a conclusion
4 that I'm going to read, "Surprisingly, the core
5 containing BHT at a concentration equivalent to
6 the two percent BHT coating had higher levels of
7 the sulfoxide degradant. Due to the instability
8 of BHT and the stability of the BHT radical
9 species, BHT radicals can enhance its oxidation
10 in the core.

11 So, Dr. Davies, if these researchers
12 had formed an a priori expectation that the known
13 antioxidant BHT could only decrease oxidation
14 rather than enhance it, they would have been
15 wrong; isn't that correct?

16 A. I don't agree.

17 Q. You don't agree with the conclusion the
18 researchers reached here?

19 A. No. I don't agree with your comments.

20 That's supposition.

21 Q. Dr. Davies, I'd now like to go and talk
22 about the parameters for the stress test that you
23 talked about on direct examination.

First, I'd like to turn to DTX 591.

1 This is a document published by the U.S.
2 Department of Health and Human Services; correct?

3 A. Yes, I agree.

4 Q. And this document sets forth guidelines
5 for stability testing of new drug substances and
6 products; correct?

7 A. That's what it says.

8 Q. And I would like to turn to Page 7 of DTX
9 591 and I'm going to blow up the tables on the
10 bottom of the page. And this table in this
11 document is describing two different tests;
12 correct?

13 A. Sorry, which page are you on? Sorry.

14 Q. Page seven.

15 A. Thank you. Yes, it is.

16 Q. One test is called long-term testing;
17 correct?

18 A. That's correct.

19 Q. And the other test is called accelerated
20 testing; correct?

21 A. That's correct.

22 Q. And for each of those tests the guidance
23 specifies a temperature at which it is to occur;
24 correct?

1 A. That's correct.

2 Q. And for each test the guidance also
3 specifies a relative humidity?

4 A. That's correct.

5 Q. And the guidance also specifies a minimum
6 time period; correct?

7 A. That is correct.

8 Q. And you agree that the tests set forth in
9 this table are standard tests; correct?

10 A. I agree they're one form of test.

11 Q. And, in fact, you believe that these are
12 standard tests within the meaning of the '031
13 patent; correct?

14 A. They're a type of test, I agree.

15 Q. And within the meaning of the '031 patent;
16 correct?

17 A. Depends what you mean by that. They're
18 certainly the kind of tests one can use and as I
19 described the process.

20 Q. And, in fact, the lower test called
21 accelerated testing, those conditions match one
22 of the two stress tests that we saw earlier that
23 were described in column four of the '031 patent;
24 correct?

1 A. That's correct, the temperature and the
2 humidity.

3 Q. But it's your opinion that the standard
4 tests that may be used for purposes of the '031
5 patent are broader than those shown in the
6 patent; is that correct?

7 A. I believe somebody skilled would
8 understand reading the patent that stress tests
9 that are described would describe such tests but
10 also would describe other tests that are known
11 stress tests that are known to pharmaceutical
12 scientists; correct.

13 Q. And if you could turn to DTX -- well, I
14 believe -- could you find JTX 75 in the binder
15 that you used on direct examination.

16 A. Thank you.

17 Q. This is the Alsante reference you talked
18 about; correct?

19 A. That's correct.

20 Q. And when I asked you earlier about
21 identifying a reference that described using a
22 forced degradation study to determine if a
23 compound was an antioxidant, you referenced the
24 Alsante reference. I would like you to tell me

1 if you can find the word "antioxidant" anywhere
2 in this document?

3 A. Well, the document doesn't mention the
4 word antioxidant. As we discussed at my
5 deposition, it does mention the word excipient,
6 and antioxidant is an excipient and it talks
7 about using stress tests as I indicated in my
8 direct for the selection of more stable drugs and
9 drug formulation. It talks about drug excipient
10 compatibilities.

11 Q. Doctor, I want to blow up a section of the
12 first page of the Alsante reference in the middle
13 portion there. And there is a section within
14 this paragraph that I want to highlight. It
15 starts at the beginning, because the ICH
16 definition leaves the details of the
17 investigation to the pharmaceutical researcher,
18 the practices that companies use to conduct
19 stress testing studies can vary tremendously and,
20 therefore, have a significant effect on the
21 quality of the analytical methodology used
22 throughout the industry.

23 You believe that what Alsante has
24 reported here is a correct characterization of

1 the use of the stress testing; correct?

2 A. Well, I think it's saying what I indicated
3 with that, with guidance from the ICH, but the
4 details are left to the individual researchers,
5 but ultimately all achieving the same objective,
6 and that's what's accepted by the FDA when they
7 review such tests.

8 Q. I would like to look at some of the
9 parameters that you went through on direct
10 examination. First on page 62 of the reference,
11 there is a sentence in here that says, pull it
12 up, the second sentence under the heading how
13 stress testing studies are conducted, says most
14 companies attempt to induce at least five to 20
15 percent degradation of the drug substance before
16 considering stress testing to be complete.

17 My question for you, Doctor, is, you
18 did not induce at least five percent degradation
19 in any of the vials in your forced degradation
20 study; correct?

21 A. That's correct, I induced about
22 three-and-a-half percent. That was sufficient
23 for me to be able to compare the two samples, the
24 control versus the acetaldehyde.

1 Q. I would like to move forward to page 67 of
2 the reference, below the heading oxidation.

3 And I would like to blow up the last
4 sentence before the heading peroxides, and that
5 sentence says, For example, in the peroxide pie
6 chart that shows typical temperatures, 84 percent
7 of the companies selected ambient to 30 degrees
8 C, 11 percent selected 31 to 50 degrees C, and
9 only five percent selected greater than 50
10 degrees C.

11 And my question for you is, Doctor,
12 in your forced degradation study, you did not use
13 a temperature that falls within what 95 percent
14 of the companies in this review selected, namely
15 a temperature somewhere between ambient and 50
16 degrees C; correct?

17 A. I agree. It fell in the range that was
18 cited within the publication.

19 Q. Now, proceeding to the first sentence
20 under the heading peroxides, the first sentence
21 says all companies use hydrogen peroxide.

22 A. That's correct.

23 Q. And you did not use hydrogen peroxide in
24 your forced degradation experiment; correct?

1 A. That's correct. That doesn't mean all
2 companies used it in every experiment, of course,
3 it just means that it's available for them to
4 use.

5 Q. The Alsante reference doesn't refer to
6 tocopherol as hydrogen peroxide; correct?

7 A. That's correct.

8 Q. Now, the last sentence of this section
9 states that the maximum study duration selected
10 was the same for one and seven days, 37 percent
11 for both. And your study duration was for less
12 than one day; correct?

13 A. It's approximately one day. It was
14 twenty-one hours, I accept that, just under one
15 day. That was sufficient for my experiment.

16 Q. The next heading on page 67 is radical
17 initiator. You did not use a radical initiator
18 in your forced degradation study; correct?

19 A. That's correct. And 15 of the companies
20 also didn't use it. You see N equals five, it
21 doesn't mean that you use it every time.

22 Q. Doctor, do you know how many different
23 radical initiators there are that you would
24 consider standard in the industry for a stress

1 test?

2 A. There could be a number. I don't know the
3 exact number.

4 Q. The next heading on page 67 is transition
5 metals. And this section describes transition
6 metals that could be used because they promote
7 oxidative degradation; correct?

8 A. That's correct.

9 Q. And there are two more categories of
10 stress tests described here for oxidation
11 purposes, pressured oxygen and bubbled oxygen;
12 correct?

13 A. That's correct.

14 Q. And you didn't use either pressured oxygen
15 or bubbled oxygen in your study; correct?

16 A. That's correct.

17 Q. Dr. Davies, if you were testing a proposed
18 antioxidant called compound X to evaluate whether
19 or not it was an antioxidant, isn't it a fact
20 that you have not considered whether doing a
21 peroxide test, a radical initiator test, a
22 transition metal test, a pressured oxygen test
23 and a bubbled oxygen test would all give you the
24 same result?

1 A. No, I don't think that's the case. I
2 think I considered that, but as I have said, you
3 design the test to address the specific drug that
4 you're looking at. And all achieve the same
5 objective if they're suitably designed. In other
6 words, they generate the oxidative degradation
7 drug.

8 Q. Doctor, I would like you to turn in your
9 deposition binder to the April 2nd, 2014
10 deposition.

11 Q. And turn to -- please turn to Page 361.
12 And I'm reading from Line 12.

13 "Question: So if you were testing a
14 proposed antioxidant, Compound X, to evaluate
15 whether or not it was an antioxidant, would doing
16 a peroxide test, a radical initiator test, a
17 transition metal test, a pressure oxygen test and
18 a bubble oxygen test all give you the same
19 result?

20 "Answer: Again, as a scientist, one
21 would -- if one doesn't know that, one would have
22 to think about that, give it some thought. It's
23 not something that I have been asked to consider.

24 But clearly these documents, as I've

1 highlighted, there's a number of different ways
2 the industry uses to undertake oxidation stress
3 tests. And the diversity reflects the diversity
4 of drugs and the different susceptibility to
5 oxidation and the different formulations."

6 Is that the answer you gave me?

7 A. Yes, absolutely. It's absolutely correct.

8 Q. And I'd like to switch topics for a
9 moment.

10 Doctor, for the batches of Par's
11 rollstock where no acetaldehyde has been
12 measured, you believe that one possible
13 explanation for why those batches contain no
14 detectable acetaldehyde is that the acetaldehyde
15 may have been consumed in an oxidation reaction;
16 correct?

17 A. Maybe I missed your question. Are you
18 saying there was a batch which -- where the
19 acetaldehyde wasn't measured, in other words?

20 Q. Let me restate the question. You remember
21 there were two batches that you talked about on
22 direct where there was not a detectable amount of
23 acetaldehyde present; correct?

24 A. Yes.

1 Q. And you believe that one possible
2 explanation for why those batches contained no
3 detectable acetaldehyde is that the acetaldehyde
4 may have been consumed in an oxidation reaction;
5 correct?

6 A. That's possible.

7 Q. It's also possible that acetaldehyde
8 evaporates; correct?

9 A. It depends. In that context, I think it
10 would be difficult because it's in the patch.

11 Q. Dr. Davies, after the Par product is
12 manufactured, isn't it true that you don't have
13 the information to know if there's any
14 acetaldehyde in the patch a month later?

15 A. Well, .

16 At one month later.

17 Q. Yes.

18 A. Certainly, there was an example of a patch
19 that I highlighted in my reports which was made
20 and then packaged one month later.

21 And that was represented to the FDA
22 as the final formulation had a level of
23 acetaldehyde. So the FDA has represented the
24 final finished product has that level of

1 acetaldehyde.

2 Q. Well, Doctor, during your direct
3 testimony, you provided testimony regarding Par's
4 specification for acetaldehyde from PTX 348. Do
5 you recall that?

6 A. Thank you. Yeah.

7 Q. And could you find Page Par 780, which is
8 where I think you got your information from?
9 Now, I'd like to blow up the entire top section.
10 Not that, the second chart, but the top section.

11 And in the method column, do you see
12 where it says Report three sample results?

13 A. I do.

14 Q. And below that, it says report results
15 from rollstock?

16 A. It does.

17 Q. And Dr. Davies, isn't it correct that you
18 have never seen a specification that requires Par
19 or 3M to measure the amount of acetaldehyde
20 directly in their finished patches?

21 A. I think this shows that it's measured in
22 the rollstock, but then Par -- Par then says to
23 the FDA -- if you look at the front of this
24 document, it says the finished product

1 specification, in other words, the finished final
2 product in the patent, in the pouch
3 specification, and it's representing that's the
4 boundaries of acetaldehyde.

5 Q. Doctor, you have never seen any data for
6 an acetaldehyde measurement taken on a finished
7 patch; correct?

8 A. I disagree. These are -- this is data
9 that is represented to the FDA on the finished
10 final products.

11 Q. My question is: You have never seen data
12 for an acetaldehyde measurement taken on a
13 finished patch; correct?

14 A. That's been taken on a finished patch.
15 This is the rolls of the stock that is then cut
16 and put into the patches. And they measure it
17 there.

18 Q. Well, let's go to your deposition, your
19 April 2nd deposition, Page 320.

20 And I'm reading from Line 6 to 12.

21 "Question: Have you seen any
22 acetaldehyde measurements that were taken on
23 finished patches?

24 "Answer: I believe the results that

1 I have seen are based on rollstock."

2 Is that the question and answer from
3 the deposition?

4 A. That's correct. That is what I said.

5 And then I go on to say, if you look
6 underneath, I've relied on Par's representations
7 of the FDA based on the acetaldehyde they
8 measured in their product. And that's what they
9 represented to the FDA.

10 That's what I just told you --
11 talked to you about. So, if you read further on
12 down the line, you know, you see exactly what I
13 just told you.

14 Q. And, Doctor, even though you asked for and
15 received 400 patches of Par's ANDA product, you
16 haven't produced any testing of the acetaldehyde
17 content of any of those patches, have you?

18 A. That's correct. I've relied on Par's
19 testing.

20 MR. BROWN: Thank you. Par has no
21 further questions.

22 THE COURT: All right. Thank you.

23 Any redirect, Ms. Jacobsen?

24 REDIRECT EXAMINATION

1 BY MS. JACOBSEN:

2 Q. Just a couple of questions, Dr. Davies.

3 Dr. Davies, do you recall Par's
4 counsel asking you questions on cross-examination
5 regarding whether you had a positive control in
6 your stress test?

7 A. Yes, I do.

8 Q. And I believe you said that you didn't
9 need to include one?

10 A. That's correct.

11 Q. And why was that?

12 A. Well, I already knew that Rivastigmine
13 would degrade, undergo oxidative degradation in
14 the presence of peroxides.

15 So I already knew that from the
16 data. And I -- my own data shows that, in fact,
17 that's exactly what happens.

18 The two key degradation products
19 that I observed are the key degradation products
20 that result from the presence of peroxide. I
21 already knew -- if I placed something, another
22 antioxidant against that system, that antioxidant
23 would have reduced the level of degradation, just
24 like acetaldehyde would. I wouldn't have any

1 other expectation because I was creating the
2 right kind of oxidative degradation.

3 Q. Dr. Davies, do you recall Par's counsel
4 asking you questions about your stress test
5 containing oxygen?

6 A. Yes.

7 Q. And would the presence of oxygen have
8 altered the results of your stress test?

9 A. No. Whether it's by oxygen or peroxides,
10 you see the same effect. You see the same two
11 key degradation products. That's what I showed
12 in my direct, that's what Par believed based on
13 their documentation as well.

14 Q. And finally --

15 A. It won't change the oxidative degradation
16 of the drug.

17 Q. And Dr. Davies, do you recall Par's
18 counsel asking you questions on cross-examination
19 about the temperature at which you conducted your
20 stress test?

21 A. Yes.

22 Q. And I believe he asked you if it was at 40
23 degrees Celsius above the boiling point of
24 acetaldehyde, do you recall?

1 A. Yes.

2 Q. Would acetaldehyde in your opinion have
3 been a gas in your stress test?

4 A. No. It would have been -- it's very much
5 present in the solution. The reason for that is
6 that acetaldehyde on its own is a pure material
7 at that particular boiling point. However, when
8 you mix it in with a solvent, it then takes the
9 -- it then alters the boiling point of the
10 material, and it's somewhere between the two
11 materials' boiling point.

12 Now, that's important because that
13 means that acetaldehyde would have stayed within
14 the solvent of my test. But then you have to
15 look at the results. Two key degradation
16 products formed and there is less formed in the
17 solvent with acetaldehyde present, showing that
18 it is present, it is acting as an antioxidant.

19 MS. JACOBSEN: Thank you,
20 Dr. Davies. I have no further questions.

21 THE COURT: Thank you. Dr. Davies,
22 you can step down.

23 Does Novartis have anything more on
24 this infringement case?

1 MS. JACOBSEN: No, Your Honor.

2 THE COURT: All right. So you rest?

3 MS. JACOBSEN: We rest.

4 THE COURT: All right. Mr. Brown.

5 MR. BROWN: Two quick things, Your
6 Honor, from Dr. Davies' cross. I again neglected
7 to admit a couple of exhibits, JTX 91 and DTX
8 591, we would like to move those for admission
9 now. It's the article and the FDA guidance.

10 MS. JACOBSEN: We have no objection.

11 THE COURT: Admitted without
12 objection.

13 MR. BROWN: DTX 591.

14 Par now calls Dr. Bruce Ganem.

15 THE COURT: All right.

16 MR. SILVER: Your Honor, one
17 housekeeping matter. We have swapped out some
18 team members. Sitting at the counsel table with
19 me will be Daniel Minion and Dominick Conde. I
20 don't know if they have been before Your Honor
21 before.

22 THE COURT: Welcome gentleman.

23 MR. SILVER: Thank you.

24 THE CLERK: Please state and spell

1 your full name for the ready.

2 THE WITNESS: Yes. My name is

3 Bruce, B-R-U-C-E, Ganem, G-A-N-E-M.

4

5 BRUCE GANEM, PH.D.,

6 the deponent herein, having first

7 been duly sworn on oath, was

8 examined and testified as follows:

9 MR. CHIN: Your Honor, may I

10 approach to pass up a pen?

11 THE COURT: Yes.

12 MR. CHIN: Your Honor, may we also

13 approach to hand up a couple of binders?

14 THE COURT: Sure.

15 DIRECT EXAMINATION.

16 BY MR. CHIN:

17 Q. Good afternoon, Dr. Ganem.

18 A. Good afternoon.

19 Q. Could you please introduce yourself to the
20 Court?

21 A. Yes. My name is Bruce Ganem. I hold an
22 endowed chair at the Department of Chemistry and
23 Chemical Biology at Cornell University in Ithaca,
24 New York. I held that chair and I also serve as

1 chair of my department.

2 Q. What is your particular focus within the
3 field of chemistry?

4 A. I'm an organic chemist and I'm
5 particularly interested in developing reaction
6 pathways to biologically active natural products.
7 That often involves developing new oxidation and
8 reduction reactions which are a core part of
9 organic chemistry.

10 Q. Could you turn to DTX 524 in your book.

11 A. Yes.

12 Q. Could you identify this document?

13 A. Yes. This is my current CV.

14 Q. Does DTX 524 provide an accurate
15 description of your professional credentials?

16 A. I believe it does.

17 MR. CHIN: Your Honor, Par moves the
18 admission of DTX 524.

19 MR. MINION: No objection.

20 BY MR. CHIN:

21 Q. Dr. Ganem, has any of your work involved
22 the development of pharmaceutical products?

23 A. Yes, it has. Several years ago my lab
24 discovered and developed a new reduction reaction

1 that has been used to greatly amplify and improve
2 the synthesis for the important anticancer drug
3 Taxol which is used in treating almost all solid
4 tumors. The drug used to come from a very rare
5 plant that was threatened biologically. We can
6 use make the drug from ordinary garden variety
7 trees, it accounts for about a third of the
8 world's supply today.

9 MR. CHIN: Your Honor, Par offers
10 Dr. Ganem as an expert in organic chemistry
11 including oxidation and reduction reactions.

12 MR. MINION: No objection, Your
13 Honor.

14 THE COURT: All right. You may
15 proceed.

16 BY MR. CHIN:

17 Q. I would like to turn to some of the issues
18 in this case. Can you explain to the Court what
19 is oxidation?

20 A. Yes. Simply put, oxidation is the process
21 by which electrons are removed from a chemical
22 compound.

Q. Can you generally describe how oxidation occurs?

1 A. Yes. Typically when a compound loses one
2 or more electrons, it transfers those compounds,
3 those electrons to another compound, a different
4 substance which accepts those electrons and is
5 thus reduced. So the process of oxidating,
6 oxidizing one compound goes hand in hand with a
7 concomitant reduction of some other substance and
8 that tandem process is generally referred to as a
9 redox process.

10 Q. Redox is short for reduction and
11 oxidation?

12 A. Yes.

13 Q. What is oxidative degradation?

14 A. So oxidative degradation is the process by
15 which the oxidation level of chemical compound
16 results in the decomposition.

17 Q. And have you prepared a slide to
18 illustrate this?

19 A. Yes, I have.

20 Q. So --

21 A. So I'll explain to the Court what I call
22 the core cycle of oxidative degradation. This
23 process begins with some organic compounds, the
24 organic compounds undergoing oxidative

1 degradation, which is oxidized by something to
2 produce this, what we call, radical.

3 But it's a chemical radical
4 different from an ordinary type of radical. It
5 has just one electron.

6 And that radical R dot will react
7 with a molecule of oxygen in the atmosphere to
8 produce another radical. This is called a peroxy
9 radical at the bottom of the slide. Both of
10 these compounds are highlighted in red because
11 they represent the process of oxidative
12 degradation.

13 Now, continuing the process in this,
14 peroxy radical encounters another organic
15 molecule such as the substance being degraded RH.
16 The peroxy radical will abstract the hydrogen and
17 be reduced, thus forming now a peroxide, a
18 hydroperoxide compound here and regenerating the
19 initial radical at the top of the slide R dot.

20 And so this process, first of all,
21 is a chain reaction. It can propagate itself
22 many, many times, going around and around this
23 cycle driving the transformation of an organic
24 compound to the oxidative degradation products.

1 It's the core engine of oxidative degradation.

2 Q. Are you aware that the Court has given a
3 definition of the term antioxidant in this case?

4 A. Yes, I am. The definition shown on the
5 slide, I understand the Court has agreed that an
6 antioxidant is an agent that reduces oxidative
7 degradation. And I have adopted that definition
8 in forming my opinions.

9 Q. Can you turn to JTX 1 in your book? This
10 is the '031 patent which has already been
11 admitted into evidence.

12 A. Yes, I'm there.

13 Q. Did you have an opportunity to study the
14 '031 patent in connection with your work on this
15 case?

16 A. I did.

17 Q. And I'd like to draw your attention to
18 Column 4, Lines 10 through 19.

19 Do you see that this passage lists
20 several antioxidant compounds that have been
21 discussed today?

22 A. Yes, it has been several times.

23 Q. In your experience, do these compounds
24 qualify as antioxidants to chemists?

1 A. Yes. They're all well-known antioxidants
2 for which extensive published literature exists.

3 Q. And can we turn back to Slide Number 2,
4 the cycle. Can you describe how the antioxidants
5 that were listed in the '031 patent act to reduce
6 oxidative degradation?

7 A. I can. So all of those antioxidants shown
8 in the '031 patent have the unique ability to
9 shut down or suppress this cycle of oxidative
10 degradation in several ways.

11 One, for example, is if the radical
12 at the top of the slide encounters a molecule of
13 antioxidant, the antioxidant will reduce this
14 radical by adding an H to it to form RH. That
15 immediately shuts down the ability of this
16 radical to drive further degradation.

17 But the unique ability of the
18 antioxidant to do that is caused by the
19 antioxidant now forming a radical, which is very
20 stable. Typically can't do anything. It can't
21 engage in the cycle.

22 So that's one example of how an
23 antioxidant can shut down this process. And
24 quickly another is simply that the antioxidant

1 can react with this red peroxy radical at the
2 bottom, get -- radical gets reduced by accepting
3 a hydrogen to form this peroxide. And, again, a
4 very stable antioxidant radical, which does not
5 contribute to oxidative degradation.

6 Q. Does aldehyde form a stable radical?

7 A. No, quite to the contrary. Acetaldehyde
8 can form a radical, but it's a highly reactive
9 radical that can itself contribute to oxidative
10 degradation.

11 Q. Can a radical of acetaldehyde break this
12 cycle of oxidative degradation?

13 A. No, quite to the contrary. An
14 acetaldehyde radical can actually engage in much
15 of this same process and enhance oxidative
16 degradation.

17 Q. You're aware that plaintiffs are
18 contending that acetaldehyde is an antioxidant?

19 A. Yes, I am.

20 Q. Did you find acetaldehyde listed in the
21 '031 patent as an antioxidant?

22 A. No, I did not find it anywhere in the
23 patent.

24 Q. How commonly is acetaldehyde used as a

1 reagent in chemical reactions?

2 A. Well, as we heard earlier today,

3 acetaldehyde is a well-known chemical compound.

4 And organic chemists use acetaldehyde all the

5 time as a synthetic building block for preparing

6 other compounds.

7 Q. In your 40 years of experience as a

8 chemistry professor, have you ever heard of

9 acetaldehyde reported as an antioxidant?

10 A. No, never.

11 Q. In your opinion, is acetaldehyde an

12 antioxidant?

13 A. No, it is not and chemists do not consider

14 it to be an antioxidant.

15 Q. Is acetaldehyde a reducing agent?

16 A. Yes, it is.

17 Q. What does it mean to be a reducing agent?

18 A. So, for a substance to be a reducing agent

19 that simply means that it will reduce some other

20 chemical substance and, in turn, become oxidized

21 as would happen in any combined redox process.

22 Q. In your opinion, does acetaldehyde qualify

23 as an antioxidant because it can be a reducing

24 agent?

1 A. No, not at all. Lot of compounds can be
2 reducing agents, but that does not mean that they
3 can disrupt this engine, this cycle of oxidative
4 degradation.

5 Q. In your opinion, does acetaldehyde qualify
6 as an antioxidant because it can be oxidized
7 itself?

8 A. No, not at all.

9 Q. What can happen if acetaldehyde is
10 oxidized itself?

11 A. Well, if acetaldehyde gets oxidized, as I
12 mentioned before, it can do so by forming a
13 reactive free radical and in turn actually
14 enhance oxidative degradation.

15 Q. Is that behavior reported anywhere?

16 A. Well, yes. We've heard in the courtroom
17 today mention that acetaldehyde can form a
18 reactive peroxide.

19 It turns out whenever you purchase a
20 sample of acetaldehyde, it comes with a serious
21 warning label that indicates the potential for
22 peroxide formation to occur and the compound
23 should be treated accordingly. The mechanisms by
24 which that happens have been well worked out in

1 the chemical literature.

2 Q. Can you turn to JTX 086 in your book?

3 A. Yes, I'm there.

4 Q. Do you recognize this document?

5 A. I do. This is a review article I've
6 relied on that describes the chemical mechanisms
7 by which acetaldehyde undergoes oxidation.

8 Q. What journal is it from?

9 A. This is from the journal Chemical Reviews,
10 which is the principal review journal of my
11 professional society, American Chemical Society.

12 MR. CHIN: Your Honor, Par moves the
13 admission of JTX 086.

14 MR. MINION: No objection.

15 BY MR. CHIN:

16 Q. Can we turn to Page 335 and have the
17 chemical equations presented on the screen?

18 Dr. Ganem, can you describe for the
19 Court what these equations show?

20 A. Yes, I can. So I direct the Court's
21 attention to a series of chemical equations
22 numbered four through eight. And these react --
23 these equations indicate that the process by
24 which an aldehyde here shown on the left of

1 equation four, RCHO can undergo an oxidation
2 using molecular oxygen to form what turns out to
3 be a variety of reactive chemical radicals.

4 So with Mr. Smith's help, I'll try
5 to highlight these for the Court. The first
6 radical, reactive radical that's formed is a
7 radical R dot shown here on the right side of the
8 equation four. That radical can then react as
9 shown in equation five with molecular oxygen to
10 form this radical peroxy radical in equation
11 five, which is another reactive radical.

12 In fact, these are the very same
13 radicals we saw in that oxidative cycle I
14 mentioned. But, furthermore, we see the
15 formation of acyl RCO. That's RCO dot on
16 equation six, and it appears again on the product
17 side of equation eight.

18 Thank you.

19 And in addition an acyl radical can
20 combine with molecular oxygen to form this
21 reactive radical shown on the right side of
22 equation seven. So we see here four different
23 chemical radicals. One of them appears twice in
24 the overall cascade of reactions. All of which

1 are reactive enough to contribute to oxidative
2 degradation.

3 Q. How do all of these reactive radicals
4 generated by acetaldehyde compare to the
5 oxidative degradation cycle that you described
6 earlier?

7 A. Well, as I mentioned, at least two of them
8 are chemically equivalent to the two that we saw,
9 and others, such as this peroxy radical is
10 similar in structure, the one on equation seven
11 is similar in reactivity and structure to the one
12 on equation five and I think chemist consider
13 acetaldehyde an extremely reactive radical.

14 Q. Do you recall that Dr. Davies mentioned a
15 negative 30 degree threshold that's mentioned in
16 the Chemical Reviews article in his testimony this
17 morning?

18 A. Yes, I do recall that. Dr. Davies pointed
19 out something having to do with a low temperature
20 limit to what's possible here. But actually he
21 was quoting from some studies that lead to this
22 understanding of reactive pathways. That
23 temperature threshold has nothing to do with
24 these equations. All of these processes can

1 occur readily at room temperature.

2 Q. Are the chemical reactions that you
3 discussed here consistent with acetaldehyde being
4 a reducing agent?

5 A. Yes, they are. Because to be a reducing
6 agent means that the compound gets oxidized. And
7 if you look overall at what happens, an aldehyde
8 such as acetaldehyde shown here at the start is
9 eventually converted into a peroxy carboxylic acid
10 shown here at the product of equation eight. So in
11 sum the reaction is a net oxidation of the
12 aldehyde.

13 Q. Are the chemical reactions that you have
14 discussed and shown here consistent with
15 acetaldehyde being an antioxidant?

16 A. No, I don't think so. As I say, this
17 process is producing a variety of quite chemical
18 radicals that would not suppress oxidative
19 degradation, they would actually enhance and
20 contribute to it.

21 Q. I would like to change to a slightly
22 different topic. Were you in court -- you were
23 in court earlier today when Dr. Davies described
24 his experiment testing, rivastigmine and

1 acetaldehyde in the presence of TBHP?

2 A. Yes, I was here throughout that.

3 Q. Have you had an opportunity to study the
4 data and records relating to Dr. Davies's
5 experiment?

6 A. I did.

7 Q. Do you consider Dr. Davies's experiment to
8 be an appropriate model for the oxidative
9 degradation of rivastigmine by oxygen?

10 A. No, I don't. And the reason I don't is
11 because Dr. Davies doesn't use oxygen in his
12 study, he uses TBHP, the peroxide compound.

13 Q. How is TBHP different than oxygen?

14 A. TBHP is different from molecular oxygen in
15 several ways. To begin with, TBHP seeks out
16 negative charge, TBHP is also a protic, meaning
17 slightly acidic compound whereas molecular oxygen
18 has no property. As we heard earlier today, TBHP
19 is a liquid whereas we're all familiar with the
20 fact that oxygen is a highly diffusible gas.

21 Q. Do those differences effect the oxidation
22 process?

23 A. Yes, they certainly can. Among other
24 things, TBHP, the hydroperoxide can perform

1 direct oxidation of chemical compounds. For
2 example, TBHP will directly oxidize an aldehyde
3 such as acetaldehyde to a carboxylic acid and TBHP
4 will directly oxidize amine such as rivastigmine
5 to the amine oxide.

6 Q. Can you describe these direct reactions
7 that you just alluded to?

8 A. Yes, I have them on a slide for the Court.
9 So on the top slide I show acetaldehyde
10 undergoing a known reaction with TBHP in which
11 the aldehyde gets oxidized to acetic acid. And
12 at the bottom of the slide I show rivastigmine
13 pointing especially to the nitrogen on the right
14 side of this molecule which undergoes an
15 oxidation with TBHP to form the amine oxide that
16 we heard about.

17 Q. How important are these direct reactions
18 under the conditions of Dr. Davies's experiment?

19 A. So as I said, in Dr. Davies's experiment
20 he used a very large excess of TBHP, so given
21 that, I would have assumed that these are the
22 dominant processes in his reaction, that
23 oxidation by air would play a minimal role, if
24 any, in his experiments.

1 Q. Does Dr. Davies's experiment reflect how
2 acetaldehyde would affect oxidative degradation
3 of rivastigmine by oxygen?

4 A. No, as I just said, there is very little
5 oxygen in Dr. Davies's experiments. In fact, I
6 was able to calculate that the amount of oxygen
7 in the experiment he described is about
8 approximately two orders of magnitude less than
9 the amount of TBHP that he put into his
10 experiments. So again, I would assume that it
11 would be very unlikely that in the Davies
12 experiments one is seeing very much oxidation
13 caused by molecular oxygen.

14 Q. Is the Davies' experiment an appropriate
15 model for oxidative degradation by oxygen?

16 A. No, for that reason, I don't think so.

17 Q. Have you reached any conclusions regarding
18 the design and methodology of Dr. Davies's
19 experiment?

20 A. Yes. So in my opinion Dr. Davies's
21 experiment is not a scientifically valid way to
22 test the oxidation of rivastigmine by oxygen. It
23 first of all -- or the effect of acetaldehyde on
24 that process.

1 Q. What is your concern about the scientific
2 validity that you just alluded to?

3 A. Well, I have several concerns. To begin
4 with, Dr. Davies does not use any method,
5 Dr. Davies's experiment doesn't use any method I
6 have ever encountered, any valid scientific
7 method that I know of to test for the antioxidant
8 capabilities of a chemical compound. But putting
9 that aside, there are additional concerns I have
10 in both the execution and methodology of his
11 experiment.

12 Q. What would be needed for a validated
13 scientific method in such a study?

14 A. Well, I think the Court has heard this
15 already this morning, and I don't want to bore
16 you, Your Honor, but the fact is in my opinion, a
17 scientifically -- for a test of an antioxidant to
18 be a scientifically valid method, the test should
19 first of all show that known antioxidants display
20 the expected antioxidant behavior that's been
21 reported for them, and likewise, compounds that
22 are known not to have any antioxidant activity
23 should be shown in the Davies test likewise to
24 exhibit no such activity. And absent those

1 controls, those validations, I don't think one
2 can draw any conclusions from an experiment.

3 Q. You also referred to issues of
4 methodology. What were you concerned about
5 there?

6 A. Well, I have three main concerns and I
7 have summarized them for the Court on a slide.

8 So to begin with, in my opinion,
9 Dr. Davies fails to account for numerous other
10 components that are produced in his reaction, and
11 in particularly, those that might be generated by
12 side reactions with TBHP.

13 Secondly, Dr. Davies in my opinion
14 fails to account for the possibility of what is
15 called co-elution of these other components in
16 the HPLC. And finally, it's my opinion that
17 Dr. Davies has improperly used a form of data
18 normalization that I believe obscures errors in
19 his experiments and actually represents them as
20 real results.

21 Q. Perhaps we can start with the first bullet
22 point. Can you explain why you consider failing
23 to account for other components to be a flaw in
24 the experiment?

1 A. Yes, I can. So Dr. Davies's bases his
2 entire analysis on the assumption that only three
3 chemical substances are involved in his
4 experiment. The rivastigmine, which he recovers
5 unreacted and the two impurities we have heard
6 about, impurity 4 and ECAV.

7 However, when we look at
8 Dr. Davies's data in the test samples, the A1,
9 A2, and A3 samples and look at the HPLC
10 chromatogram of those experiments, one sees
11 numerous other minor compounds that show up as
12 peaks in the chromatogram all across the
13 chromatogram. And Dr. Davies simply ignores
14 these other compounds and does not characterize
15 them. He, I think to put it harshly, he pretends
16 they don't exist and bases his analysis only on
17 three compounds I mentioned.

18 Q. Did Dr. Davies attempt to address your
19 criticism about ignoring other components?

20 A. I raised this concern in one of my expert
21 reports and Dr. Davies replied as I think we
22 heard him say today, that he could account for 99
23 percent of the mass in his experiment. He
24 referred to that as a 99 percent mass balance.

1 When I looked at his data with that
2 in mind, I discovered that Dr. Davies
3 inappropriately included a large solvent peak
4 that is used, you used solvent to inject your
5 HPLC sample into the chromatogram. I think he
6 inappropriately included that solvent in his mass
7 balance.

8 MR. MINION: Objection.

9 THE COURT: Yes.

10 MR. MINION: It seems like Dr. Ganem
11 is offering a sure reply to Dr. Davies's reply
12 report. He only has one main expert report.

13 MR. CHIN: Your Honor, Dr.

14 MR. CHIN: Your Honor, Dr. Ganem had
15 a couple of different paragraphs explaining the
16 missing other components. Dr. Davies responded
17 in his surreply. I think Dr. Ganem is entitled
18 to explain why he believes it, in his opinion
19 that he sets forth, is a valid opinion in light
20 of Dr. Davies' response --

21 THE COURT: Was his response before
22 the two professors were deposed?

23 MR. CHIN: All of this was prior to
24 the deposition. There were three reports.

1 Dr. Davies set forth his experiment.

2 Dr. Ganem set forth his criticisms. And then and
3 only then did Dr. Davies say he had an
4 appropriate mass balance.

5 Then depositions were taken. That's
6 the record. If we had to have a surreply for
7 every single response to a response, I don't
8 think we'd ever end up submitting expert reports.

9 THE COURT: Well, that's probably
10 true. So basically what you are saying, what I'm
11 about to hear is not in any expert report.

12 THE COURT: Well, that's --

13 MR. CHIN: The substance of it is in
14 the expert report, Dr. Ganem set forth his
15 criticism of the lack of accounting for other
16 components and he merely explained why that is an
17 appropriate criticism in light of what Dr. Davies
18 said in his rebuttal report and his last three
19 reports before depositions.

20 We're not getting into any new data.

21 They're not getting into any new substance.

22 THE COURT: You have something more
23 to say?

24 MR. MINION: I do. I want to say

1 two things: That what he was going into, what
2 Dr. Ganem was about to go into talking about, the
3 solvent peak and that wasn't in any of the
4 reports, not in Dr. Davies' report, not in
5 Dr. Ganem's report.

6 And I would like to point out that
7 after the depositions were over, Dr. Ganem did
8 supplement his expert report and he did not put
9 this new opinion in.

10 THE COURT: Is that right, Mr. Chin?

11 MR. CHIN: It was a one-page
12 supplemental to make some minor corrections to an
13 entirely unrelated issue. This issue did not
14 occur and it was to correct an error that was
15 raised during the deposition.

16 THE COURT: All right. Well, I
17 think you -- what you can actually do, you can
18 probably make a point of what he made in his
19 report, first report. So why don't you stick to
20 that.

21 So I'll sustain the objection.

22 MR. MINION: Thank you, Your Honor.

23 MR. CHIN: If you can just give me a
24 minute to --

1 THE COURT: Yes.

2 MR. CHIN: -- find the precise
3 language of the original report.

4 BY MR. CHIN:

5 Q. Dr. Ganem, can you describe for me
6 approximately how much of the non-volatile
7 analytes that Dr. Davies failed to account or
8 correct for?

9 A. Yes, I think I can. In Dr. Davies'
10 experiment, it was about 92 to 93 percent of a
11 material that was unreactive Rivastigmine. That
12 leaves about seven or eight percent for the
13 impurities of the reaction product.

14 But what Dr. Davies failed to
15 account for, about one-fifth of that -- 20
16 percent.

17 Q. And what conclusions do you draw from
18 failing to account for about one-fifth of the
19 impurities?

20 A. Well, my concern as a scientist is that a
21 large amount of undocumented material, it goes
22 unrecognized. Some of this could have been
23 formed, as I mentioned already, by the side
24 reactions or direct reactions of TBHP with --

1 with these impurities, Impurity 4 and ECAV.

2 The net result of that is that it
3 would alter the -- it would distort the actual
4 percentages of those two impurities. And I
5 believe this is important because, as we heard
6 earlier today, Dr. Davies experiment relies on
7 measuring minute differences between these
8 impurity peaks, Impurity 4, ECAV and I'm
9 concerned that these other components could have
10 distorted that.

11 Q. Dr. Ganem, have you served as an editor or
12 a reviewer for peer-reviewed journals in the
13 chemistry literature?

14 A. Yes, for over a dozen years, I was the
15 U.S. executive editor for a journal called
16 International Journal of Organic Chemistry.

17 We typically handle about 500 papers
18 a year in that office.

19 Q. In your opinion, would a scientific study
20 that fails to account for other components in the
21 system, as you discussed, be acceptable for
22 publication in a peer-reviewed journal?

23 A. No, generally not.

24 Q. Let's turn to your second bullet point,

1 the co-elution issue that you mentioned. Can you
2 describe why you believe failure to account for
3 co-elution of these components is a flaw in the
4 Davies experiment?

5 A. Yes. Well, as I just described to the
6 Court --

7 THE COURT: Can you first describe
8 what co-elution is?

9 THE WITNESS: I'll describe that.
10 Give me just a moment.

11 THE COURT: Okay.

12 THE WITNESS: So I mentioned there
13 was about 20 percent of these other products that
14 went uncharacterized. And when one looks at one
15 of the HPLC chromatograms that Dr. Davies did in
16 this experiment, these other minor things are
17 spread across the entire spectrum frequently
18 bracketing one on either side of a peak of
19 interest, such as Impurity 4 of ECAV.

20 Now, sometimes they're so close that
21 the tail of one peak begins to merge a rise of
22 another peak. That is, they overlap.

23 And when peaks overlap like this,
24 the possibility exists of co-elution, which means

1 the two different compounds are coming out
2 together, at least in part. That's what
3 co-elution is and it's not an uncommon experience
4 of HPLC analysis, especially when peaks are close
5 together.

6 So the concern I have about this
7 co-elution, different compounds showing up in the
8 same peak, is that this is another factor that
9 can distort the actual amount of a particular
10 impurity. It could either contribute to or
11 detract from the actual amount of the compound
12 that's present.

13 And I think any good scientist would
14 be concerned about that when, again, the
15 differences being measured are such minute
16 percent differences between control experiments
17 and the test experiments.

18 Did I explain co-elution for you?

19 THE COURT: Yes. I get it. Yes.

20 BY MR. CHIN:

21 Q. Now, you heard this morning how Dr. Davies
22 had identified the peaks, Impurity 4 and ECAV.
23 Does that account for collusion?

24 A. So I raised this concern about co-elution.

1 This is one of my replies to Dr. Davies and he
2 responded, first of all, by saying in the case of
3 ECAV, he had taken a UV spectrum. We heard him
4 testify to that today.

5 Now, a UV spectrum will tell you
6 whether you have the compounds you believe you
7 have. But other components can be present in a
8 sample without -- that would not distort the
9 ultraviolet spectrum. So that's not a very good
10 explanation or response to my concern.

11 It indicates of Impurity 4, pardon
12 me, the other impurity Dr. Davies responded
13 simply by saying that he had shown that was ECAV
14 by using an authentic standard. And I understand
15 that, but that doesn't diminish the possibility
16 of co-elution. So he really did not address my
17 concerns.

18 Q. And, finally, if we can turn to the third
19 bullet point, improper data normalization. Can
20 you explain why you find that to be a flaw in the
21 experiments?

22 A. Yes, I can. And to do so, it helps if I
23 can show Dr. Davies' summary of his own data on a
24 slide.

1 Thank you.

2 So this is from Dr. Davies' summary
3 of his experiment in which he reports the results
4 of his three control experiments, the absence of
5 acetaldehyde and in the presence of acetaldehyde.

6 And we see he's measuring the three
7 compounds I have spoken about, Rivastigmine,
8 Impurity 4 and ECAV.

9 Now, Dr. Davies, I've already
10 pointed out, I think, has erroneously decided to
11 ignore these other minor peaks. But to make
12 matters worse, he simply shows the yields of
13 these three compounds in a way that they all add
14 up almost magically to a perfect hundred-percent
15 yield. And he achieves this by a process of data
16 normalization.

17 It's a simple arithmetic maneuver
18 that takes the sum of each of the -- the sum of
19 all the areas of these peaks and calls that 100
20 percent. And then you take a fraction of each of
21 these and you guarantee that the yields will turn
22 out to be 100 percent.

23 My concern about this is that this
24 maneuver, this arithmetic maneuver can easily

1 hide serious flaws in the data.

2 Q. In actuality, accounting for all of the
3 material, including impurities in the test tubes,
4 has he, in fact, accounted for a hundred percent?

5 A. Well, I think by this mathematical
6 slight-of-hand, it looks as though he has
7 accounted for everything. But if you look at the
8 chromatogram, these are these other unidentified
9 peaks that

10 I've mentioned.

11 Q. Now, you had indicated that this technique
12 has a potential to hide significant errors. Did
13 you see any specific examples of errors in
14 technique?

15 A. Actually I did. Yes, I did.

16 And it's the same error Mr. Brown
17 pointed out earlier today, but I won't insult the
18 Court by showing the data that I'm particularly
19 concerned about. It was the A3 sample at 15
20 hours.

21 If Mr. Smith can pull that up for
22 me. Thank you.

23 This is from his Appendix E, his
24 summary of his experiment. Here are the

1 individual tubes for A3 taken, I believe, at the
2 15-hour point where we've already heard that
3 Dr. Davies got a raw measurement of the
4 Rivastigmine at about 6,937 units, which he
5 pointed out represented a 98.39 percent yield.

6 Then, if we compare this tube A3
7 data to the 21-hour point, the same tube at 21
8 hours, as we've already heard, has almost
9 magically increased in the raw data, accounts for
10 Rivastigmine by about 50 percent to 10,185.

11 So once sees 50 percent increase in
12 the area for that peak. But in the normalized
13 yield calculation, we magically see the yield go
14 from 98.39 down to 97.74.

15 Now, as a journal editor or an
16 author, if I had a data point like this, this
17 would immediately be tossed out because clearly
18 something went very wrong in this experiment.
19 And yet, it was included in Dr. Davies final
20 analysis. This is inappropriate, in my opinion.

21 Q. When you received Dr. Davies' final
22 analysis with his opening expert report, did it
23 acknowledge this problem?

24 A. No, but I asked him about it. I raised

1 this point in my reply report and he responded,
2 as we heard mentioned earlier today, that one
3 explanation might be a loose seal on this tube,
4 which would lead to solvent evaporation and a
5 concentration effect that would increase the
6 measured area in this loosened tube.

7 Q. Is it appropriate to include such data in
8 the calculations?

9 A. No. I think this data point should have
10 been tossed out. But, more importantly, the
11 concern I have is that if the tube was leaking,
12 one could confidently assume that some
13 acetaldehyde would escape from that tube. It
14 would be a high vapor pressure of acetaldehyde at
15 60 degrees. And over a prolonged period of time,
16 I would think a substantial amount of
17 acetaldehyde would have escaped along with
18 solvent. So that totally compromises this
19 experimental data point.

20 Q. Taking into account the issues you've
21 discussed about study design and methodology, in
22 your opinion, can Dr. Davies' experiment be
23 scientifically relied upon to show that
24 acetaldehyde is an antioxidant?

1 A. In my opinion, given the concerns that
2 I've raised, I don't think any scientifically
3 valid conclusions could be drawn from the
4 experiment run by Dr. Davies.

5 MR. CHIN: Thank you, Dr. Ganem.

6 THE COURT: I'm sorry, sir. Can you
7 just tell me your name again?

8 MR. MINION: Dan Minion.

9 THE COURT: Minion. Thank you.

10 Mr. Minion, you may proceed

11 CROSS-EXAMINATION

12 BY MR. MINION:

13 Q. Good to see you again, Dr. Ganem.

14 A. Good afternoon, Mr. Minion. Good to see
15 you, too.

16 Q. So let's you and I talk a little
17 chemistry. Okay?

18 A. Happy to do so.

19 Q. All right. You agree that Rivastigmine is
20 susceptible to oxidative degradation?

21 A. Yes.

22 Q. And there's no question it's established
23 scientifically that Rivastigmine undergoes
24 oxidative degradation to form ECAV in Impurity 4?

1 A. Yes, I would agree with that.

2 Q. Can you put -- thank you.

3 You recognize this slide, Dr. Ganem?

4 A. I think this may have been an earlier
5 slide shown today. I certainly recognize the
6 compounds. Yes.

7 Q. All right. Dr. Davies walked through
8 this.

9 He talked about the pathway of
10 oxidative degradation of Rivastigmine.

11 A. Yes.

12 Q. And you recognize the oxidative
13 degradation impurities ECAV and Impurity 4?

14 A. I do recognize them.

15 Q. Those are the correct structures of those
16 compounds?

17 A. Yes, I believe so.

18 Q. And the first step of the oxidative
19 degradation pathway that Dr. Davies walked
20 through is an oxidation of Rivastigmine to the
21 amine oxide. That's what he has there; correct?

22 A. That's correct.

23 Q. And that is the same structure that you
24 had in on your slide showing the reaction of

1 rivastigmine with tertbutyl hydroperoxide?

2 A. Correct, I pointed out that's the product
3 with direct oxidation.

4 Q. Once the amine oxide is formed, it's
5 eliminated to ECAV?

6 A. Yes, that's a good technical term. It's
7 an elimination reaction.

8 Q. And then it's further oxidized to impurity
9 4?

10 A. Yes. Dr. Davies said that this is one
11 path to ketone, to the ketone shown as impurity
12 four.

13 Q. One of the ways that antioxidants work is
14 by undergoing oxidation themselves before the
15 compound they are protecting; correct?

16 A. That's one mechanism, yes.

17 Q. That's how reducing agents like ascorbic
18 acid work?

19 A. Agreed.

20 Q. You noted in your direct examination you
21 looked at the specific antioxidants that are
22 listed in the '031 patent?

23 A. I acknowledged the ones that are listed
24 there.

1 Q. You saw ascorbic acid on the list?

2 A. I believe so.

3 Q. That's a well-known antioxidant?

4 A. Yes, it is. It's vitamin C.

5 Q. It's a reducing agent?

6 A. Yes.

7 Q. And, of course, ascorbic acid is

8 susceptible to oxidation?

9 A. Yes.

10 Q. And when ascorbic acid acts as an

11 antioxidant, it sacrifices itself by being

12 preferentially oxidized over the compound that it

13 protects?

14 A. I would agree that ascorbic acid acts as

15 an antioxidant by getting oxidized, yes.

16 Q. And you agree that any chemical compound

17 that is a known reducing agent must, in fact, be

18 subject to oxidation?

19 A. Well, that's a bit flowery language, but

20 yes, all reducing agents do get oxidized.

21 Q. And you agree that acetaldehyde is

22 susceptible to oxidation?

23 A. I do.

24 Q. And I believe when you were going through

1 the photo chemical degradation of acetaldehyde in
2 the McNesby article, you commented that
3 acetaldehyde is oxidized readily at room
4 temperature?

5 A. I think what I said was that my opinion
6 these reactions to form these radicals could
7 occur at room temperature, yes, I may have said
8 readily.

9 Q. That's the oxidation of acetaldehyde by
10 air?

11 A. I think what I said yes, the radicals
12 would form under air oxidation fairly readily.

13 Q. And acetaldehyde can be oxidized by
14 peroxides?

15 A. Yes.

16 Q. For example, you noted that acetaldehyde
17 can be oxidized by tertbutyl hydroperoxide?

18 A. That's correct.

19 Q. You will agree by the very fact that
20 acetaldehyde can be oxidized, it is capable of
21 acting as an antioxidant?

22 A. I'm not sure what you mean capable,
23 counselor. We know that an antioxidant works by
24 getting oxidized, so to be -- if a compound is a

1 reducing agent, it has potential to be an
2 antioxidant.

3 Q. But you never actually studied the
4 potential role of acetaldehyde as an antioxidant?

5 A. No, I never conducted any experiments.

6 Q. And in forming your opinions in this case,
7 you did not consider whether acetaldehyde can
8 function as an antioxidant?

9 A. I'm sorry, would you repeat your question?

10 Q. In forming your opinions, you did not
11 consider whether acetaldehyde can function as an
12 antioxidant?

13 A. Well, I think the question that you asked
14 and can be answered by saying acetaldehyde can be
15 oxidized, so that means that at least it meets
16 the minimal requirement that it could function as
17 an antioxidant. I think even Dr. Davies conceded
18 that point.

19 Q. But in forming your opinions, you set out
20 to establish that acetaldehyde cannot function as
21 an antioxidant for rivastigmine?

22 A. I'm not sure. I honestly am not sure how
23 to answer your question. I'm not sure I
24 understand what you're driving at.

1 Q. We talked about this at your deposition,
2 right, the question of whether acetaldehyde can
3 function as an antioxidant and whether
4 acetaldehyde cannot function as an antioxidant in
5 your opinion, those are distinctly different
6 questions?

7 A. Yes, that's fine.

8 Q. And the question that you set out to
9 answer to establish was that acetaldehyde cannot
10 function as an antioxidant for rivastigmine?

11 A. I think it's correct to say I did consider
12 that question. I tried to consider both sides of
13 the question in forming my opinion.

14 Q. So you did a literature search to find
15 some basis to support your opinion that
16 acetaldehyde cannot be an antioxidant for
17 rivastigmine. Do you remember that search?

18 A. I think I do, yes.

19 Q. And as a result of those searches, you put
20 forth an opinion regarding the oxidation
21 potential of those two compounds, acetaldehyde
22 and rivastigmine?

23 A. Well, I did. But as you know, I withdrew
24 my report on that, that section of my report

1 because of an error I made.

2 Q. We're going to get to your supplemental
3 report, but let's go back to your original
4 opinion. We're talking about oxidation
5 potentials. You talked a little bit about redox
6 reactions in your direct examination?

7 A. I did, but I did not mention oxidation
8 potentials in my exam.

9 Q. You agree that an oxidation potential is
10 the tendency of a compound to be oxidized?

11 A. Yes.

12 Q. In other words, the higher the compounds
13 oxidation potential, the more easily it's
14 oxidized?

15 MR. CHIN: Your Honor, I have an
16 objection. I think this is going beyond the
17 scope of direct.

18 THE COURT: I'll allow it.

19 BY MR. MINION:

20 Q. Do you want me to give you that one again?

21 A. Yes, please.

22 Q. Talking about oxidation potentials. The
23 higher, the more positive the compound's
24 oxidation potential, the more easily the compound

1 can be oxidized?

2 A. That's generally true, yes.

3 Q. So if a compound has a more positive
4 oxidation potential compared to another compound,
5 that means it's more easily oxidized?

6 A. Well, as you know, counselor, we have to
7 be concerned about these being measured under
8 identical conditions, but if you want me to
9 stipulate that in fact we're talking about
10 oxidation potentials being measured under
11 identical conditions using identical electrodes,
12 then what you say is generally true.

13 Q. Now, you provided an opinion that
14 acetaldehyde cannot function as an antioxidant
15 for rivastigmine because acetaldehyde has a lower
16 oxidation potential than rivastigmine?

17 A. You know, I don't recall exactly how I
18 phrased it, but as I told you, I made a
19 conversion error when I did some of my
20 calculations and I quickly withdrew my report
21 when I found my error.

22 Q. I have your report. Do you need to
23 refresh your recollection of what your opinion
24 was?

1 A. Well, since I withdrew that section of my
2 report, I'm not sure why we're talking about it.

3 Q. I said we're going to get to your
4 supplemental report in a minute, but I want to
5 talk about the way you set out in your opinions
6 in this case, and we'll come there eventually,
7 but in your original opinion you looked in the
8 literature to look at oxidation potentials and as
9 a result of that analysis, you set forth an
10 opinion that acetaldehyde cannot function as an
11 antioxidant for rivastigmine because acetaldehyde
12 has a lower oxidation potential than
13 rivastigmine?

14 A. Okay. So if you allow me to stipulate
15 again that we're talking about an opinion that I
16 later withdrew, I think that is what I had in my
17 original report, yes.

18 Q. You were comparing standard oxidation
19 potential, or you thought at the time you were
20 comparing standard oxidation potentials?

21 A. That's correct.

22 Q. And you looked in the literature and you
23 determined that the standard oxidation potential
24 of acetaldehyde is 0.60 volts?

1 A. I think that may have been the number,
2 yes.

3 Q. But you weren't able to find any reference
4 providing an oxidation potential for
5 rivastigmine?

6 A. That's correct. So far as I could tell,
7 the oxidation potential for rivastigmine was not
8 available in the literature, so I found several
9 analogous compounds in forming my opinion.

10 Q. Was that the Lindsay Smith article?

11 A. Yes, I believe so.

12 Q. And the Lindsay Smith article talks about
13 oxidation potentials of N-N dimethyl benzyl
14 amines, substituted N-N dimethyl benzyl amines?

15 A. I believe that's correct.

16 Q. And those share a similar chemical
17 structure to rivastigmine?

18 A. Yes. They would have just this, just this
19 part right here, not that part.

20 Q. But in the Lindsay Smith article where
21 rivastigmine has the carbamate functionality, the
22 Lindsay Smith article had like trifluoromethyl and
23 nitro and different substituted N-N dimethyl
24 benzyl amines?

1 A. Honestly, counselor, I don't recall. It's
2 been over a year since I looked at the Lindsay
3 Smith article and as I pointed out several times,
4 once I withdrew my opinion, I have not considered
5 that article any further.

6 Q. Okay. I agree. I have your expert report
7 if you have to refresh your recollection at any
8 time, just let me know.

9 Now, you looked at the Lindsay Smith
10 article and you calculated the oxidation
11 potential of rivastigmine to be between 1.0 and
12 1.05 volts, higher than that of acetaldehyde?

13 A. I honestly don't remember what I
14 calculated from a year and three months ago. As
15 I say, this is ancient history and I assume when
16 I withdrew my report that that would indicate
17 that I was not offering that opinion.

18 Q. You recall that you calculated the
19 oxidation potential of rivastigmine to be higher
20 than that of acetaldehyde?

21 A. I think that's correct. What I was
22 calculating was an estimate for rivastigmine
23 based on the analogs in that paper.

24 Q. But your calculation was wrong?

1 A. I did use a conversion factor incorrectly,
2 yes.

3 Q. You added when you should have subtracted?
4 A. It was a mistake which I quickly withdrew
5 my opinion.

6 Q. When you subtracted instead of added, you
7 discovered that the calculated oxidation
8 potential for rivastigmine was .52 to .57?

9 A. Again, I don't remember the number, but
10 the relative position of the numbers changed,
11 yes.

12 Q. And as you have mentioned, subsequent to
13 your deposition you have withdrawn the section of
14 your expert report relating to oxidation
15 potentials?

16 A. Yes, after I discovered my error, I simply
17 withdrew that report, that opinion, that section
18 of my report.

19 Q. Because the Lindsay Smith article does not
20 provide a valid basis for comparison of
21 rivastigmine and acetaldehyde?

22 A. Well, I withdrew it because in the end
23 there was just too much uncertainty to draw any
24 solid conclusion that I felt I could rely on.

1 Q. Because the Lindsay Smith article talks
2 about oxidation peak potentials?

3 A. As I said, I realized I could not make a
4 comparison that would be reliable one.

5 Q. Getting back to the question of whether
6 acetaldehyde is an antioxidant, you testified
7 that the sacrificial oxidation of acetaldehyde
8 could promote the oxidation of other compounds?

9 A. That's not quite correct, counselor. I
10 simply testified that the oxidation of
11 acetaldehyde, I have not spoken about sacrificial
12 oxidation today.

13 Q. But your opinion is that if acetaldehyde
14 is oxidized, it might form a peracid compound?

15 A. If acetaldehyde is oxidized, it is known
16 to form a peracid, yes.

17 Q. But you agree that acetaldehyde can also
18 be oxidized to acetic acid?

19 A. Yes, that's true.

20 Q. And acetaldehyde?

21 A. And acetaldehyde can also be reduced.

22 Q. And acetic acid is not a known oxidizing
23 agent; right?

24 A. No, that wouldn't be correctly true.

1 Acetic acid could be an oxidizing agent and it
2 would in turn be reduced to, for example,
3 acetaldehyde or even to ethyl alcohol.

4 Q. You agree that acetic acid is not a free
5 radical?

6 A. Acetic acid per se is not a free radical,
7 that is correct.

8 Q. And you're not aware of any testing that
9 shows that acetaldehyde increases the oxidative
10 degradation of rivastigmine?

11 A. No. As I said, I did not conduct any
12 testing on my own.

13 Q. And you did not opine in your expert
14 report that acetaldehyde was acting as a
15 prooxidant based on Par's stability testing data?

16 A. I made no mention of prooxidants anywhere
17 in my reports, in my report.

18 Q. You did not opine that acetaldehyde could
19 promote the oxidation that -- actually let me
20 rephrase that.

21 You did not opine that acetaldehyde
22 promotes the oxidative degradation of
23 rivastigmine based on Par's stability testing
24 data?

1 A. From what I know of Par's stability
2 testing data, acetaldehyde does absolutely
3 nothing at all.

4 Q. Now, you said you acknowledge that you
5 didn't do any testing in this case?

6 A. Well, first of all, I did, I did
7 acknowledge that. I wasn't asked to consider
8 doing that, and because of conflict rules at my
9 university, I'm not permitted to do that.

10 Q. So you had several criticisms in your
11 direct examination of Dr. Davies's methodologies?

12 A. Yes, these were technical criticisms.

13 Q. Now, you could have as a scientist gone
14 through and repeated Dr. Davies's stress test?

15 A. Well, I have explained why I really can't
16 do that at Cornell.

17 Q. So in this case, you were prevented from
18 repeating Dr. Davies's stress test?

19 A. Well, I'll try to be as clear as I can.
20 My university considers external consulting
21 activities like these to be the sort of things
22 I can't use university resources for, it's a
23 conflict of interest and a conflict of
24 commitment. See I just can't do it, and I'm the

1 head of my university's conflict committee so I
2 have to set a good example.

3 Q. You could have asked someone else to do
4 it; right?

5 A. I'm not sure what you mean by that. I
6 can't ask anyone at my university to do it. I
7 couldn't ask one of my graduate students to do
8 it.

9 Q. You could have asked someone outside of
10 the university?

11 A. I guess I could have. I didn't consider
12 that.

13 Q. Well, let's come at it a different
14 direction. Notwithstanding your agreement with
15 the university, if you had permission to repeat
16 Dr. Davies's tests, you could have done so?

17 A. Oh, it's not technically difficult, that's
18 true, I could have done it.

19 Q. And you would have had ample time to
20 repeat those tests?

21 A. Well, from what I heard about the time
22 Dr. Davies spent doing it, if I had the protocol
23 available, it doesn't sound like it would take a
24 lot of time. I'm just not sure it would be the

1 appropriate test to do.

2 Q. But someone other than you could have
3 rerun these tests to see if they could isolate
4 and characterize any other degradation products
5 besides ECAV and Impurity 4 in the reaction
6 mixtures?

7 A. I think Dr. Davies could have done that,
8 too, he just chose not to.

9 Q. Anyone on Par's side could have done that
10 as well?

11 A. I can't speak for Par.

12 Q. And someone could have repeated Dr. Davies
13 experiments to see -- to answer your question of
14 whether there were any other co-eluting compounds
15 in the peaks of ECAV and Impurity 4?

16 A. I think that would be straightforward.

17 Q. But as far as you know, that wasn't done?

18 A. Insofar as I know.

19 Q. You talked about potential errors in
20 Dr. Davies's test. You're not a statistician,
21 are you?

22 A. No, I'm not.

23 Q. And determining whether differences in
24 oxidative degradation products between two

1 samples -- sorry, determining whether the
2 differences in oxidative degradation products
3 between two samples were statistically
4 significant is not an area you have done much
5 work in?

6 A. Correct.

7 Q. And you didn't conduct any independent
8 statistical analyses of Dr. Davies's data?

9 A. That's right.

10 Q. But you did have the underlying data?

11 A. I had the data that was presented, I think
12 it's called appendix E, Dr. Davies's experimental
13 report.

14 Q. All right. So let's talk about tests to
15 determine whether a compound in a transdermal
16 formulation is acting as an antioxidant. Am I
17 correct that it is your opinion that the only way
18 to determine if a compound in a transdermal
19 device is acting as an antioxidant is to conduct
20 a stability experiment comparing two sets of
21 patches, one set of patches that contain the
22 compound and one set of patches that did not
23 contain the compound?

24 A. So you asked me that question in my

1 deposition, and at the time it was an entirely
2 hypothetical question. If you don't mind my
3 reminding you, you didn't mention what we were
4 testing. You didn't mention what the control and
5 test would be. And I think I answered by saying
6 it would be desirable to set up the test that
7 way, yes.

8 Q. Desirable to set up the test with one set
9 of patches that contain the compound in question
10 and one set of patches that didn't?

11 A. Yes.

12 Q. And you testified that in your opinion to
13 be a valid test, the two sets of samples should
14 be made identically?

15 A. I believe what I said was that would be
16 desirable, yes.

17 Q. At the same manufacturing site?

18 A. I think I said that, yes.

19 Q. Using the same process?

20 A. May I finish?

21 Q. Go ahead, sir.

22 A. I said that it would be desirable. Thank
23 you.

24 Q. Using the same processes?

1 A. Yes, that's likely what I said.

2 Q. And having both sets of materials made
3 using the same batches of starting materials?

4 A. I said that would also be desirable.

5 Q. From the same lot numbers?

6 A. If possible, yes.

7 Q. But the bottom line is that the two sets
8 should be made under virtually identical
9 conditions?

10 A. Well, just to be clear, I said you know,
11 one is faced with designing this hypothetical
12 test with, you know, no specific compounds being
13 named, it was compound A I think we used at my
14 deposition, I said it would be desirable to try
15 to achieve those goals if possible, yes.

16 Q. That the patches should be made under
17 virtually identical conditions?

18 A. As close as possible I said would be
19 desirable, yes.

20 Q. To have a valid test to determine whether
21 the antioxidant is functioning, whether the
22 compound is functioning as an antioxidant?

23 A. Well, I think again, we were talking about
24 testing a patch for an unspecified property and I

1 said that that would be desirable.

2 Q. And without having two identical sets of
3 patches, one set with the compound, and one set
4 without the compound, you cannot think of a way
5 of determining whether the compound is acting as
6 an antioxidant?

7 A. I don't recall saying that.

8 MR. MINION: Sorry, Your Honor. May
9 I approach.

10 THE COURT: You may.

11 THE WITNESS: Thank you, Your Honor.

12 MR. MINION: I'm very sorry.

13 BY MR. MINION:

14 Q. Take a look at page 127, line five.

15 A. Okay.

16 Q. "Question: Just like your original
17 methodology, that methodology requires a second
18 batch of patches that do not contain the alpha
19 tocopherol?

20 "ANSWER: Correct.

21 "QUESTION: Now, if you're not
22 provided a second batch of patches that have no
23 alpha tocopherol, in your opinion, is there any
24 valid way of determining whether alpha tocopherol

1 is acting as an antioxidant in the composition?

2 "ANSWER: No, not that I can think
3 of."

4 MR. CHIN: Your Honor, I think the
5 basis of this testimony is talking about that
6 methodology that they had discussed previously,
7 just earlier in the deposition.

8 THE COURT: All right. You can
9 bring it up on redirect.

10 Go ahead, Mr. Minion.

11 BY MR. MINION:

12 Q. Those are the questions and answers that
13 you gave in your deposition?

14 A. Yes. Thanks for refreshing my memory.

15 MR. MINION: I have no more
16 questions, Your Honor.

17 THE COURT: All right. Mr. Chin,
18 how convenient.

19 REDIRECT EXAMINATION

20 BY MR. CHIN:

21 Q. Dr. Ganem, when Mr. Minion was asking you
22 about that methodology in your deposition, what
23 was he referring to?

24 A. I believe he was referring to a more or

1 less entirely hypothetical question about patches
2 being tested. And I might have to refresh my
3 memory.

4 Q. If you can just explain, in a general
5 sense, I guess or perhaps I can --

6 MR. MINION: Objection, Your Honor.

7 I object that the witness is reading from his
8 deposition.

9 THE WITNESS: Well, I'm not supposed
10 to read from the deposition?

11 MR. CHIN: I'll just rephrase the
12 question.

13 THE COURT: All right. Go ahead,
14 Mr. Chin.

15 BY MR. CHIN:

16 Q. Was Mr. Minion asking about Rivastigmine?

17 A. No.

18 Q. Was Mr. Minute asking about any type of
19 Par product?

20 A. No.

21 Q. Was Mr. Minion asking about FDA
22 guidance-related products?

23 A. No, he was not.

24 Q. Was it a hypothetical situation?

1 A. Yes, it was a hypothetical situation. He
2 was careful to structure his question that way.

3 Q. Mr. Minion, during his cross-examination,
4 made reference a couple times to sacrificial
5 oxidation. Have you seen any evidence in this
6 case or heard any evidence from Dr. Davies that
7 acetaldehyde undergoes sacrificial oxidation?

8 A. I only heard Dr. Davies this morning
9 mention that a compound that is a reducing agent
10 undergoes sacrificial oxidation. And that is not
11 my understanding of the definition of reducing
12 agent and no freshman chemistry student would
13 accept that, either.

14 The reducing agent refers to a
15 compound that simply undergoes oxidation.
16 There's no restrictive adjective that goes along
17 with that word oxidating.

18 Q. Mr. Minion also asked you about the issue
19 of oxidation potentials that was raised earlier
20 on in this case. And you, I think, had indicated
21 that you had made or the corrections were needed
22 to conversion of oxidation potentials.

23 Based on the corrected oxidation
24 potentials, was there any information that you

1 saw that suggested that acetaldehyde is an
2 antioxidant?

3 A. No. And as I say, when I discovered my
4 error, misapplying this correction factor, I
5 withdrew my opinion on that matter.

6 Q. I believe Dr. Klibanov had responded to
7 your expert report on the issue of oxidation
8 potentials?

9 A. Yes, he did. Dr. Klibanov, whom I know,
10 also -- well, perhaps I can only say that he made
11 no mention of any misapplication or correction
12 factor so it went undetected until my deposition.

13 Q. Both you and Dr. Klibanov missed the
14 conversion?

15 A. Apparently so.

16 MR. CHIN: I have no further
17 questions.

18 THE COURT: All right. Thank you,
19 Mr. Chin.

20 Dr. Ganem, you can step down.

21 THE WITNESS: Thank you.

22 THE COURT: So why don't we take our
23 afternoon break of 15 minutes and come back then
24 at about somewhere between ten and five of 4:00

1 to finish out for the day.

2 THE CLERK: All rise.

3 (A brief recess was taken.)

4 THE CLERK: All rise. All right
5 please be seated. Mr. Fineman.

6 MR. FINEMAN: Yes, Your Honor. We
7 have a short housekeeping matter on
8 confidentiality, Your Honor.

9 THE COURT: Okay.

10 MR. FINEMAN: I believe that during
11 Dr. Davies' examination, two exhibits were used
12 JTX 065 and JTX 200.

13 And we've conferred with 3M and we
14 would like to place those exhibits under seal and
15 3M would like to reserve the right to review the
16 transcript and then propose redactions.

17 THE COURT: I'm sorry, that cannot
18 be right. What were the exhibit numbers?

19 MR. FINEMAN: I have written down
20 JTX 065 and JTX 200.

21 THE COURT: G?

22 MR. FINEMAN: J, Joint Trial.

23 THE COURT: Sorry. Sorry.
24 You say 65 and 200?

1 MR. FINEMAN: That's correct, Your
2 Honor.

3 THE COURT: All right. So we'll put
4 them under seal.

5 We'll place them under seal and 3M
6 can look at the transcript and weigh in on that
7 in due course. Okay.

8 MR. FINEMAN: Yes, Your Honor. And
9 when Dr. Dizio is testifying, there will be a use
10 of JTX-065 again; however, this one will have --
11 this will not be the same copy of JTX-065 that
12 plaintiff was using because this is with the --

13 THE COURT: Redactions?

14 MR. FINEMAN: Exactly.

15 THE COURT: Right.

16 MR. FINEMAN: More accurate, Your
17 Honor, less than complete.

18 THE COURT: Okay. All right.

19 MR. FINEMAN: And we'll work that
20 out.

21 THE COURT: Okay. Well, that's
22 good.

23 MR. FINEMAN: Thank you, Your Honor.
24 Your Honor, at this time, Par calls James Dizio.

1 THE COURT: All right.

2 MR. FINEMAN: Your Honor, I'm
3 informed that it was not 200. It was 177.

4 THE COURT: Okay.

5 THE CLERK: Can you state and spell
6 your full name for the record.

7 THE WITNESS: My name is James Dizio.

8 It's J-A-M-E-S D-I-Z as in zebra I-O.

9 THE CLERK: Please place your left
10 hand on the Bible and raise your right hand.

11

12 JAMES DIZIO,

13 the witness herein, having first
14 been duly sworn on oath, was examined
15 and testified as follows:

16 THE CLERK: Thank you. Please be
17 seated.

18 MR. FINEMAN: Your Honor, permission
19 to approach?

20 THE WITNESS: Thank you.

21 DIRECT EXAMINATION

22 BY MR. FINEMAN:

23 Q. Good afternoon, sir.

24 A. Good afternoon.

1 Q. Could you please introduce yourself to the
2 Court?

3 A. Yes. I'm James Dizio.

4 Q. Could you please briefly describe your
5 educational background?

6 A. Yes. I have a B.S. degree in civil
7 engineering. I worked as a mechanical engineer
8 for about four years and then I went back to
9 school and got a Ph.D. in organic chemistry,
10 synthetic organic chemistry from the University
11 of Illinois, one of the top schools in the
12 country for that type of chemistry.

13 Q. Where are you currently employed?

14 A. 3M. It's a great company.

15 Q. How long have you been employed by 3M?

16 A. Well, since 1991, so 23 years.

17 Q. What position do you hold at 3M?

18 A. I'm a lead chemist in the materials
19 resource division.

20 Q. What are your responsibilities as lead
21 chemist in the materials resource division?

22 A. I -- I -- you know, I invent, develop, and
23 I scale molecules and polymers for, you know, all
24 of 3M's business divisions. 3M has many business

1 divisions.

2 The materials resource division is
3 like 3M's internal chemical company.

4 Q. Does any of your work relate to
5 pharmaceutical products?

6 A. Yes. You know, in the last few years,
7 I've been focusing on medical products in
8 general. You know, U.S. population is getting
9 older. I don't want to say anybody in here, but
10 the U.S. population is getting older, and you
11 know, 3M is the perfect place. I mean it.

12 3M is the perfect place to innovate
13 for this population and we are.

14 Q. Do these pharmaceutical products include
15 transdermal drug delivery patches?

16 A. Yes.

17 Q. Can you please describe 3M's experience
18 with transdermal drug delivery patches?

19 A. Yes. 3M -- 3M is an innovator in these
20 patches. I'd say 3M has been working in
21 transdermal patches for probably 30 years.

22 And so, you know, we've made
23 single-layer patches. We've made multilayer drug
24 in adhesive patches, and I'd say that the patches

1 we make are industry standards.

2 Q. Does 3M engage in FDA good manufacturing
3 practices with respect to medicinal products such
4 as transdermal drug delivery products?

5 A. Yes, we have. You know, yes, and we
6 follow every FDA guideline.

7 We follow good manufacturing
8 practices. And by good manufacturing practices,
9 it's a detailed way to do procedures. You know,
10 3M makes a lot of products.

11 We make a lot of products. But when
12 it comes to medical, there's good manufacturing
13 practices. And that's a cut above industry
14 practice.

15 You have to be very detailed so, and
16 we actually surpassed all the requirements we're
17 asked to do and we surpass them. You know, we
18 surpass them because we want to. And we surpass
19 them because it's good for the customer.

20 And, you know, the customer knows
21 that and that's why they buy from 3M.

22 Q. Now, Dr. Dizio, I'd like to turn your
23 attention to 3M's Rivastigmine transdermal patch
24 and its development?

1 A. Yeah.

2 Q. Were you involved in the development of
3 the Rivastigmine transdermal patch product that
4 3M developed that's the subject to this
5 litigation?

6 A. Yes. Yes.

7 I developed the adhesive system 3M
8 cleverly calls it R-217149.

9 Q. What was your role?

10 A. My role is to -- is to develop and scale
11 the R-27149 for a variety of drugs that we're
12 looking at.

13 Q. How did you first become involved with the
14 Rivastigmine transdermal patch product?

15 A. I was approached by the drug delivery
16 systems. So, again, 3M has many different
17 companies, in essence, that we all work together.

18 One was called drug delivery systems
19 division. And I was approached by people there
20 and they said, "Hey, Jim, can you make an
21 adhesive for these variety of drugs that we're
22 looking at making patches for?" And I said,
23 "Yes. I certainly can."

24 Q. What requirements, if any, did the drug

1 delivery systems division communicate to you
2 about the adhesive they were looking for?

3 A. Well, it's a variety of requirements with
4 a delivery patch. First and foremost, the drug
5 has to be stable to live in the patch. It has to
6 be compatible with the patch.

7 And, you know, you want to -- so
8 that -- well, that you know you need to figure
9 out what monomers go into that polymer, so that
10 adhesive will be compatible. So that's number
11 one.

12 Then you have to think about
13 molecular weight. You know, when they formulate,
14 you wouldn't want the patch slipping all around
15 your skin. That's not going to be any good.

16 You have to make sure the polymer
17 you can get of a certain molecular weight, and
18 it's got to be a polymer, which we can
19 sufficiently clean. You can't clean every
20 polymer, so we know and we are very serious about
21 this.

22 In 3M, if you're going to work on
23 medical product, you're going to use an
24 exceptionally clean adhesive. So it's got to be

1 an adhesive where you design this thing such that
2 it can be cleaned. And we do that.

3 We do that especially because when
4 you clean that adhesive, then you can, for drug
5 delivery systems for formulators, they can
6 minimize what goes into that formulation because
7 they're quite stable.

8 Q. How did you go about achieving an
9 exceptionally clean adhesive?

10 A. As I was -- well, you -- well, okay. So
11 you make a polymer.

12 And when you say make a polymer, I
13 mean, you start with the parts. They're called
14 monomers. And you have an initiator.

15 This initiator starts the chain
16 reaction that makes this big polymer. But when
17 you're done with that, you know there's going to
18 be monomers, initiators left. They're
19 impurities. They're residuals.

20 And there's things, side reactions
21 you don't know about. And you just want to get
22 rid of them.

23 So we wash the material, a washing.
24 So we clean the materials such that there's only

1 polymer left. And then many times, we will
2 distill solvent, so we can get rid of any boilers
3 or we can adjust the solvent system.

4 MR. FINEMAN: Your Honor, at this
5 time, we respectfully ask that the Court close
6 the courtroom to the public and to those not
7 entitled to access to 3M's highly confidential
8 information for a brief period.

9 THE COURT: All right. So I would
10 ask anybody who's not sitting at counsel table or
11 otherwise designated to please leave the
12 courtroom. I don't think, based on what I've
13 been told, this is going to be more than fifteen
14 minutes.

15 All right. So I see outside experts
16 on one side who I recognize, outside experts that
17 I'm guessing on the other side, attorneys that I
18 recognize, 3M, there is people over there, but --
19 so we're good; right?

20 MR. FINEMAN: Yes, Your Honor.

21 THE COURT: Go ahead, Mr. Fineman.

22 MR. FINEMAN: Thank you, Your Honor.

23 BY MR. FINEMAN:

24 Q. Dr. Dizio can you please turn to JTX 177

1 in your binder?

2 A. I'm there.

3 Q. Do you recognize this document?

4 A. Yes. Yes. This is the drug master file
5 which we call the DMF. This is the DMF for
6 solvated acrylate copolymer adhesive, R-27149.

7 Q. Is R-27149 the adhesive in the
8 rivastigmine transdermal patch that 3M makes?

9 A. Yes.

10 MR. FINEMAN: Your Honor, since I
11 not sure if JTX 177 is in the record, at this
12 time to the extent it's not in, Par moves the
13 admission of JTX 177.

14 MR. MINION: No objection.

15 THE COURT: If it's not admitted,
16 it's admitted without objection.

17 BY MR. FINEMAN:

18 Q. What does this document generally
19 describe?

20 A. This document would describe the adhesive
21 R-27149 and the process it uses to make it.

22 Q. Did you draft any parts of this document?

23 A. Yes, I submitted drafts for sections two
24 and three.

1 Q. Can you please turn to section three on
2 page 25614 entitled synthetic route of
3 manufacture?

4 A. I'm there.

5 Q. Can you please describe the steps
6 described in the DMF and manufacture of the
7 R-27149 in general terms?

8 [REDACTED]

9 [REDACTED]

10 [REDACTED]

11 [REDACTED]

12 [REDACTED]

13 [REDACTED]

14 [REDACTED]

15 [REDACTED]

16 [REDACTED]

17 [REDACTED]

18 [REDACTED]

19 [REDACTED]

20 [REDACTED]

21 [REDACTED]

22 [REDACTED]

23 [REDACTED]

24 [REDACTED]



1 [REDACTED]
2 [REDACTED]
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5 [REDACTED]
6 [REDACTED]
7 [REDACTED]
8 [REDACTED]
9 [REDACTED]
10 [REDACTED]
11 [REDACTED]
12 [REDACTED]
13 [REDACTED]

14 Q. Did you reach a conclusion of what is the
15 effect of the washing distillation steps?

16 A. Yes, the effect is to clean the polymers
17 substantially so that it meets the specs, it
18 doesn't have residuals, doesn't have initiators,
19 it doesn't have things you're not looking for.
20 You're left with polymer.

21 Q. Is the commercial manufacturing process
22 described in the DMF the process that 3M used to
23 prepare the R-27149 adhesive contained in the
24 rivastigmine transdermal patch product that 3M

1 developed?

2 A. Well, now you're getting exact. And yes,
3 it is. It is the process. But we reserve the
4 right to change some temperatures slightly and to
5 change time slightly because like we said, we're
6 looking for a certain way, we're looking for
7 certain viscosities, we're looking for certain
8 percent solids, so we may change some
9 temperatures slightly to get it.

10 Q. Did you develop this manufacturing
11 process?

12 A. Yes.

13 Q. Has 3M filed any patent applications on
14 this manufacturing process?

15 A. Yes.

16 Q. Can you please turn in your binder to JTX
17 017, and when you get there, sir, my question is,
18 do you recognize this document?

19 A. I'm there. And I do recognize the
20 document. This is the patent application
21 WO-2012/012417 Al, it's the patent application for
22 the process we just discussed.

23 MR. FINEMAN: At this time, Your
24 Honor, Par moves the admission of JTX 017 into

1 evidence.

2 MR. MINION: No objection, Your
3 Honor.

4 THE COURT: It's admitted.

5 BY MR. FINEMAN:

6 Q. Are you a named inventor on this patent
7 application?

8 A. Yes.

9 Q. Can you please turn to the general and
10 detailed descriptions of the copolymer solvent
11 washing process on page 17 of the application?

12 A. I'm there.

13 Q. Did you draft these section of the patent
14 application?

15 A. Yes, I submitted drafts. These are the
16 drafts.

17 Q. Do these sections describe the washing and
18 distillation steps in the manufacturing process
19 3M used to prepare the R-27149 adhesive?

20 A. Where in general, yes, they describe the
21 process that then went to the manufacturing
22 plant. These actually when you look at the
23 numbers, like if you look at line number 13, it
24 says a hundred grams of copolymer A is added

1 to -- a hundred grams, that's my lab.

2 So it's not the manufacturing, it's
3 not 10,000 pounds, so yes, this is a general
4 description of what went to the manufacturing
5 plant, but these actually describe my own bench
6 scale or lab scale experiments.

7 Q. Now, do you have an understanding that
8 there is a contention that rivastigmine
9 transdermal patch product 3M developed contained
10 acetaldehyde?

11 A. Yes. But acetaldehyde would be an
12 impurity to us. We're looking to get rid of
13 impurities.

14 Q. Where does that acetaldehyde come from?

15 A. It's an impurity that comes from the
16 manufacturing of the polymer, specifically one of
17 the parts is vinylacetate and that vinylacetate
18 can have side reactions that create acetaldehyde,
19 the impurity.

20 Q. Does 3M ever add acetaldehyde to its
21 R-27149 adhesive for the rivastigmine transdermal
22 patch that 3M developed?

23 A. No, absolutely not.

24 Q. I want to put JTX 065 up on the screen and

1 bring up table one on page 721. And I would like
2 to walk you through some of the information here,
3 if that's okay with you, Dr. DiZio?

4 A. Ready.

5 Q. Do you see the batch that has 300 parts
6 per million acetaldehyde?

7 A. Yes.

8 Q. Do you see the comments in the table?

9 A. There is various comments. I see the
10 comment on the right-hand side and left, yes.

11 Q. What, if anything, do the comments in the
12 table tell you about this batch?

13 A. Well, if you -- okay. If you go to the
14 first column, you'll see in parenthesis, 236.
15 That is a batch number for a polymer made in the
16 manufacturing plant. And if you go to the very
17 right, you'll see the words unwashed adhesive.
18 So this is, you know, how I described it, you
19 make, you wash, and you distill. This is to
20 make. And it means we did not wash it, nor
21 distill it, but it is made in the manufacturing
22 plant, it's just not washed.

23 Q. And what about the batches below this one
24 that contain between 211 and 402 parts per million

1 adhesive lot. What if anything do the comments
2 in the table tell you about those batches?

3 A. Again, if you look at the acetaldehyde,
4 the first column, this is a suffix, ED 2. So
5 that's me, and so that is my lab scale first ever
6 made batch. In fact, there wasn't even a process
7 back then. This is the first time I ever tried to
8 make, wash the material. I didn't even distill
9 it. So this is my first ever experiment. And so
10 it's a lab scale, bench scale wash, but really the
11 way I wash it, I wash it well, I got
12 to admit, I do wash it well, but you know, this
13 is a very viscous polymer, so when I'm washing it
14 and trying to get the methanol to interact with
15 the polymer, I'm shaking it by hand, I'm not
16 doing a very good job, or I'm not doing as good a
17 job as the manufacturing plant can do.

18 It's indeed a good job, but it's not
19 like the manufacturing plant. I don't have the
20 equipment. So this is my first ever material.
21 It's not distilled, either.

22 Q. Are there any of the batches in this table
23 representative of the process that's described in
24 the DMF in your patent application?

1 A. Yes. The lots 20,007 and 20,008, if you
2 look on the first column. So I picked those
3 because those are manufacturing batches, they're
4 lots seven and eight, so you know, we got pretty
5 good at making this after a few batches, right,
6 you can't look at the first batches, but you can
7 certainly look at the most recent batches, and
8 lot seven and eight, we would have gotten pretty
9 good at washing and distilling and doing this
10 process in the plant so they would be the most
11 representative on this page of a manufacturing
12 plant.

13 Q. How does the manufacturing scale process
14 differ from your bench scale process?

15 A. Well, the manufacturing process can do
16 much better job in intimately washing this
17 material. Imagine, you know, when I'm in my lab,
18 you can image like I'm doing a good job, but I'm
19 not like a great washing machine. This in this
20 plant there are these big impellers that just
21 beat the heck out of this polymer and intimately
22 mix it with the washing solution and therefore
23 you can get a much better washing of the polymer.
24 In my lab I can do a good job, but the

1 manufacturing plant can do a better job.

2 Q. Does 3M prepare batches for commercial
3 marketing on the bench scale?

4 A. No.

5 MR. FINEMAN: Thank you, Dr. DiZio.

6 No further questions at this time.

7 THE COURT: Thank you, Mr. Fineman.

8 Mr. Minion.

9 MR. MINION: Thank you, Your Honor.

10 BY MR. MINION:

11 Q. Hi, Dr. DiZio.

12 A. Hi.

13 Q. Let's talk a little bit more about your
14 involvement with the R-27149 adhesive. It's my
15 understanding you began working on the R-27149
16 adhesive around five years ago?

17 A. That's about correct, yes

18

19 Q. And prior to that, you had never developed
20 an adhesive for use in a transdermal product?

21 A. That's correct. I developed adhesives for
22 the many business divisions in 3M and this would
23 have been my first drug delivery one.

24 Q. You don't know who actually first

1 synthesized the R27149 adhesive?

2 A. I know that representatives of materials
3 resource division made the polymer years ago, the
4 unwashed version.

5 Q. And so you testified you looked to the
6 DMF. You testified that the R27149 adhesive is
7 washed?

8 A. The R27149 adhesive is washed and
9 distilled. Yes.

10 Q. And it's washed until specifications are
11 met?

12 A. Yes. It is washed until specifications
13 are met.

14 Q. But you don't know the specification for
15 acetaldehyde in the R27149 adhesive?

16 A. Well, the washing process, in general,
17 we're washing to get out -- actually the beauty
18 of the way we wash, it's expensive and we pay for
19 it, and the beauty of it is that you wash out
20 things that you know about, which we're checking
21 for and things we didn't know about. So we know
22 we're getting rid of almost any impurity.

23 Q. Well, let me take a step back. R27149
24 adhesive is washed?

1 A. Yes.

2 Q. All right. Not for a set number of times?

3 A. The DMF shows three times.

4 Q. Right. But it's washed until the
5 specifications for the adhesive are met?

6 A. And when you rely on the process, as we
7 currently do, and you look at the data from the
8 process, it takes three washes.

9 Q. But you do not know the specification for
10 acetaldehyde in the R-27149 adhesive?

11 A. The specification for acetaldehyde, I know
12 that, once again, we are ridding the system of
13 impurities. There's -- you know, we
14 indiscriminately rid the system from impurities.

15 And --

16 Q. That's not my question. I'm asking about
17 the specific specification number for
18 acetaldehyde that's allowed in the manufacturing
19 process to be acceptable.

20 A. Well, when you look at the data that is on
21 that chart, you'll see that when we do follow
22 this process, which we have to by GMP guidelines
23 and how we've set up the DMF, we will get a
24 percentage of -- well, we'll get a certain PPMs

1 of acetaldehyde. And it's stated in that chart.

2 Q. But you don't know the number of PPMs of
3 acetaldehyde that are allowed to be in the
4 product to meet specification?

5 A. To meet specification toxicological
6 specifications, 3M has people from drug delivery
7 systems, submitted paperwork and experiments that
8 would give them toxicological limit. Now, we, in
9 the plant, we wash this baby until we meet
10 specifications from the monomers which get the
11 acetaldehyde down to levels you see in that test.

12 Q. Do you know the number for acetaldehyde in
13 the specification?

14 A. The toxicological limit?

15 Q. The amount of acetaldehyde that's allowed
16 in the product.

17 A. The -- well, you know, it's too simplistic
18 to say that. There's different reasons and
19 acetaldehyde is -- if there is a specification,
20 it is a toxicology specification.

21 So, for instance, if you say what's
22 the specification for water, oh, huge because
23 water is not toxic. And so neither is -- not
24 really is acetaldehyde.

1 Q. You've never done any testing to determine
2 the acetaldehyde content of the R27149 adhesive?

3 A. I have never done that. No.

4 Q. All right. That's because you're not an
5 analytical chemist?

6 A. Because I'm not part of that team.

7 Q. So you're not involved with the team that
8 does analytical testing of the R27149 adhesive?

9 A. I'm not part of that team. Well, I'm part
10 of the -- yes. I'm not part of the analytical
11 team. I'm part of the team from which analytical
12 is also a part.

13 Q. Understood. You mentioned that, as a
14 result of your work on the R27149 adhesive, you
15 filed a patent application?

16 A. We followed the -- we are required to
17 follow a DMF and the FDA guidelines, and so we
18 follow the DMF and FDA guidelines.

19 Q. I'm sorry. I think you misheard my
20 question.

21 I think you mentioned on your direct
22 examination that, as a result of your work on the
23 washing procedure of the R27149 adhesive, you
24 filed a patent application.

1 A. That is correct.

2 Q. Okay. Now, in that patent application,
3 there's no discussion of acetaldehyde.

4 A. It's an impurity. There's no discussion
5 of it.

6 Q. Can you put up JTX 017? Actually you
7 should have it in your binder as well, Dr. Dizio.

8 If you turn to Page 5 of the patent,
9 and you see at Line 6, it discusses what the
10 patent term, what essentially free of any added
11 antioxidant means?

12 A. Yes. I see those words.

13 Q. We've got it up here. It should be on
14 your screen as well.

15 A. Yeah.

16 Q. The patent says, "As used herein,
17 'essentially free of any added antioxidant'
18 refers to a transdermal adhesive composition to
19 which no antioxidant has been added for the
20 purpose of preventing a pharmaceutically active
21 compound susceptible to oxidative degradation
22 from forming total drug impurities in excess of
23 two percent within two years at room temperature
24 or two months at 60 degrees Celsius with ambient

1 humidity. For certain embodiments, preferably
2 less than 0.1 percent, more preferably less than
3 0.05 percent, most preferably less than 0.01
4 percent antioxidant is present in the transdermal
5 adhesive composition, which is 'essentially free
6 of any added antioxidant'".

7 Have I read that correctly?

8 A. You did.

9 Q. Now, when it says for certain embodiments
10 preferably less than 0.1 percent of antioxidant is
11 present in the transdermal adhesive. 0.1 percent
12 is a thousand PPM; correct?

13 A. That's correct.

14 Q. So a transdermal formulation containing
15 1,000 PPM antioxidant would satisfy the definition
16 in your patent application as being "essentially
17 free of any added antioxidant"?

18 A. Now, again, you're asking me about the
19 wording of the patent; right, and this isn't -- I
20 don't know. See, again, I'm not a lawyer and I
21 am a chemist and I scale things up.

22 I make sure that the customer is
23 well satisfied and the FDA is satisfied. This is
24 a paragraph in the text of a patent and I see

1 what it says.

2 And I can tell you that when it
3 comes to the process that I do in 3M for drug
4 delivery systems, I look to get rid of anything
5 and everything from that polymer. I don't look
6 to add anything. It is the spirit of what I do
7 to give clean polymer.

8 Q. I'm going to ask you some questions now
9 about the extent of your involvement with 3M's
10 Rivastigmine patches. All right.

11 We talked about your adhesive. I
12 want to talk about 3M's actual patches.

13 A. Okay.

14 Q. You're not involved with the formulation
15 of 3M's Rivastigmine patches; right?

16 A. I am part of the team and, you know, the
17 good part about 3M and I really mean this, is
18 that we trust each other. And we all have
19 different jobs to do.

20 My job is to give them the cleanest
21 reagent I can possibly give them. Why? Because
22 that simplifies their job.

23 And I trust that they do their job
24 well. So it's too simplistic to say, no, I'm not

1 involved in the patch. What is true is that I
2 give them the cleanest reagent I can possibly do
3 and that aids in their job.

4 Q. You've not been present for the
5 formulation of the adhesive or for the
6 Rivastigmine transdermal patch with its
7 components?

8 A. No, because, once again, that would cause
9 me not to work on other products in 3M. I trust
10 what my formulators are doing.

11 Q. And you never actually prepared an active
12 drug in the transdermal formulation?

13 A. No, it wouldn't be necessary.

14 Q. Including Rivastigmine?

15 A. Including Rivastigmine.

16 Q. And you've never researched whether
17 Rivastigmine is susceptible to oxidative
18 degradation?

19 A. I have not.

20 Q. And you never personally reviewed the
21 results of any stability testing on Rivastigmine?

22 A. I have not. Now, once again, you know, we
23 all work as a team. And if we all overlapped on
24 each other's responsibilities, first off, 3M

1 would not be a great company.

2 We have certain responsibilities and
3 we know -- we know what others need and we
4 deliver that. So just because I haven't done
5 that, actually that's a good thing.

6 Q. I'm trying to establish where you are in
7 the whole scheme of things.

8 A. I'm an essential part of that team as I'm
9 on many teams on 3M.

10 Q. But with respect to 3M's Rivastigmine
11 patches, you're not part of the analytical team?

12 A. I am not an analytical chemist. No.

13 Q. And you've never seen a certificate of
14 analysis for any of the batches of 3M's
15 Rivastigmine patches?

16 A. No.

17 Q. And you've not investigated the
18 acetaldehyde content of 3M's Rivastigmine
19 patches?

20 A. I have not. I look to rid the system of
21 it.

22 Q. But you don't recall seeing any data
23 related to acetaldehyde content in 3M's
24 Rivastigmine patches?

1 A. Say it again, Dan.

2 Q. You don't recall seeing data related to
3 acetaldehyde content in 3M's Rivastigmine
4 patches?

5 A. Well, that was one of the examples I just
6 saw here today. That's one of the -- I see data
7 in these hand-outs.

8 Q. That's for the adhesive. I'm talking for
9 the Rivastigmine patches.

10 A. Oh, no, I haven't seen that. Again, we're
11 looking to rid the system of impurities.

12 I think, you know -- you have to.
13 We don't want it. We don't want anything we
14 don't know about.

15 Q. I asked you about the manufacture of 3M's
16 Rivastigmine patches. You've never actually seen
17 3M's Rivastigmine patches being manufactured?

18 A. No, they are in California. I have other
19 jobs to do.

20 Q. And you've never seen a document
21 describing how 3M formulates its Rivastigmine
22 patches?

23 A. I know that the formulation is -- because
24 of what I'm giving them is probably fairly

1 simple. But, no, I would -- that would be
2 formulated in the coating plant.

3 Q. So you don't know the components of 3M's
4 Rivastigmine patches?

5 A. I know what I supply and I know that
6 because I supply an exceptionally clean adhesive
7 and that I only give them the polymer, they can
8 minimize the reagents that they put in there.

9 Q. You supplied polymer in the past; right?

10 A. I supplied polymer to drug delivery
11 systems, yes, and to other business units.

12 Q. All right. But if 3M in the future were
13 to manufacture Rivastigmine patches on behalf of
14 Par pharmaceuticals, you do not know what
15 adhesive 3M would use in that formulation?

16 A. What adhesive 3M would use?

17 Q. Correct.

18 A. That's an interesting question. I mean,
19 that's like saying if you had to start all over
20 again, what would you do?

21 I think if I had to start all over
22 again and drug delivery had to start all over
23 again, we'd do the same thing. So almost like
24 you're from drug delivery saying, Hey, Jim, let's

1 make an adhesive for a patch. We have a history
2 with a certain adhesive and we know it works.

3 So my guess is we would pick the
4 same group. Right?

5 Q. But you don't know; right?

6 A. But you don't know, either. I mean, who
7 would know?

8 It's like saying, Hey, make a patch.

9 Well, with this -- if they -- if we're going to
10 use the adhesive that we developed for this drug,
11 we're going to use the adhesive I developed.

12 Yes.

13 Q. Okay. But if 3M were to manufacture a
14 Rivastigmine transdermal formulation
15 incorporating the R27149 adhesive, you do not
16 have an understanding of how that adhesive would
17 be prepared?

18 A. I have the adhesive being prepared.
19 Again, and we have a DMF and that DMF details how
20 to do it.

21 We are going to follow that because
22 that's what we've told the FDA again it's -- and
23 it's good for the customer and I'm very proud.
24 3M is very proud of this adhesive. This is good

1 for the customer. This adhesive is exceptionally
2 clean.

3 It is a minimalist. When you make a
4 medical product, you don't want to add stuff.
5 You want to have the minimum that you possibly
6 can have.

7 It's just generally a good idea.

8 But it costs money to do it and that's why people
9 like 3M, because we spend the money to do that.

10 Q. If 3M were to manufacture Rivastigmine
11 transdermal formulation incorporating the R27149
12 adhesive, you do not have an understanding of how
13 that R27149 adhesive would be prepared in the
14 future?

15 A. I -- okay. So it's almost like you're
16 saying, Hey, anything can happen. But anything
17 can't happen. This is business.

18 In business, you've spent the money
19 to scale a product. You paid people like me and
20 my team to do an exceptional job for the
21 customer. It would be unlikely that you would
22 not go there.

23 It would -- it would be almost
24 impossible. But so I think we would use the

1 adhesive scaled for this purpose.

2 MR. MINION: No more questions, Your
3 Honor.

4 THE COURT: All right. Any
5 redirect, Mr. Fineman?

6 MR. FINEMAN: No redirect at this
7 time, Your Honor. We have no objection to
8 reopening the courtroom.

9 THE COURT: Okay. Well, let's if
10 somebody -- if I can ask Ms. Lester to go back
11 and -- in any event, Dr. Dizio, you may step
12 down.

13 THE WITNESS: Thank you. Judge, the
14 book?

15 THE COURT: Leave the book there.

16 THE WITNESS: Okay.

17 THE COURT: They'll take care of it.

18 All right. What's next?

19 MR. FINEMAN: Your Honor, at this
20 time, Par will be playing certain video
21 deposition designations. Although I think we may
22 still have a couple small issues.

23 THE COURT: All right. Well, start
24 playing them.

1 MR. FINEMAN: Thank you, Your Honor.

2 MR. SILVER: I think we may be able
3 to address them on the front end, if we can. Mr.
4 Loh is here.

5 THE COURT: All right. I'm charging
6 the time to you all.

7 So, go ahead.

8 MR. LOH: Just briefly, Your Honor,
9 the substance of the testimony that you're about
10 to see comes from an inventor and two, 30(b)(6)
11 witnesses, one Novartis, one LTS.

12 It's not clear from opposing counsel
13 what they intend to use the testimony for. They
14 indicated it's both for infringement and
15 validity. Based on the substance, we believe
16 it's probably more related to validity.

17 And, as Your Honor knows from the
18 pretrial order in this case, those issues are
19 written description, definiteness and enablement.
20 Each of these inquiries is one that is assessed
21 from the objective standpoint of the person of
22 ordinary skill in the art. And it's from his
23 perspective looking at the '031 patent and the
24 disclosures therein.

1 The testimony that you're going to
2 see is about what the inventors, Novartis and LTS
3 did and believed before the '031 patent was even
4 filed by the Patent Office. So, for that reason,
5 we'd submit that the deposition testimony that
6 you're about to see is, in fact, irrelevant to
7 the validity issues in this case.

8 Additionally, to the extent that
9 they're going to transform this fact testimony
10 into opinion testimony relating to the person of
11 ordinary skill in the art used, we don't think
12 there's a foundation for that. And so we think
13 this testimony is also improper opinion testimony
14 and there's no foundation to offer this
15 particular testimony as that of the person of
16 ordinary skill.

17 That's the basis for our objection.

18 THE COURT: All right. Well, I'm
19 going to overrule your objections, not because I
20 think you're misstating the law, but because I'm
21 going to charge the time of playing this to Par.
22 If it turns out to be irrelevant, tough. Then,
23 it's just irrelevant.

24 MR. LOH: Understood. Thank you,

1 Your Honor.

2 MR. FINEMAN: Your Honor, I think
3 there is an issue with one counter designation in
4 the third deposition, the Ogorka deposition while
5 we're --

6 THE COURT: Why don't we play the
7 first two deposition and then I'll hear you on
8 the third one.

9 MR. FINEMAN: I was going to say I'm
10 going to try to work it out with Mr. Silver while
11 we're playing it.

12 THE COURT: All right. Even better.

13 (Beginning of videotape deposition
14 excerpt:)

15 Q. Can you state your name for the record?

16 A. Harry Tiemessen.

17 Q. But you're aware that antioxidants act as
18 reactive oxygen scavengers?

19 MR. MINION: Objection to form.

20 THE WITNESS: I think I heard of
21 that, yes.

22 Q. Dr. Tiemessen, you've been handed what's
23 been marked as Tiemessen Exhibit Number 20, Bates
24 labeled N0257460 through N0257466; is that

1 correct?

2 A. That's correct.

3 Q. And this is United States Patent Number
4 6,316,023; is that right?

5 A. That's right.

6 Q. Are you familiar with this document?

7 A. Yes.

8 Q. And are you listed as an inventor on this
9 patent?

10 A. That's correct.

11 Q. If I could direct you to Column 4 of the
12 patent, which is N0257462.

13 A. Which column?

14 Q. Column 4.

15 A. Four, okay.

16 Q. Line 14, it states, "The applicant has
17 found that an effective stabilizing effect is
18 surprisingly achieved when the antioxidant is
19 selected from tocopherol, esters thereof, e.g.,
20 tocopherol acetate, ascorbyl palmitate acetic
21 acid, butylhydroxytoluene, butylhydroxyanisole or
22 propyl gallate, preferably alpha tocopherol or
23 ascorbyl palmitate."

24 Did I read that correctly?

1 A. You read that correctly.

2 Q. And so there's a listing here of
3 antioxidants; is that correct?

4 A. That's correct.

5 Q. And as those compounds are antioxidants, a
6 pharmaceutical formulator would understand that
7 those compounds can be added to a formulation to
8 stabilize that formulation; is that correct?

9 MR. MINION: Objection to form.

10 THE WITNESS: These antioxidants,
11 they can be used in a certain set of
12 circumstances for certain compounds, certain
13 formulations to -- to stabilize and to reduce the
14 level of oxidation.

15 Q. And a --

16 A. But it's not -- not that you take just one
17 and put them in and it works. That is not the
18 case. It can even be worse if you add an
19 antioxidant. So this is high level of
20 fine-tuning that's required on that.

21 Q. Did Sandoz or Novartis ever test any
22 antioxidants listed here for use in the
23 rivastigmine transdermal system other than alpha
24 tocopherol and ascorbyl palmitate?

1 A. Not that I'm aware of.

2 Q. We talked just a bit a few minutes ago --
3 well, you said that Novartis never assessed acetic
4 acid, butylhydroxytoulene, butylhydroxyanisole,
5 propyl gallate. How do you know that those
6 antioxidants would have a stabilizing effect on
7 rivastigmine?

8 MR. MINION: I object as outside the
9 scope of the 30(b) (6) notice.

10 (Witness peruses the exhibit.)

11 MR. MINION: And to form.

12 THE WITNESS: I think it have to be
13 investigated.

14 Q. So you're not aware -- I'm sorry. You're
15 not aware of any if the antioxidants in that list
16 other than alpha tocopherol, would have a
17 stabilizing effect on rivastigmine in a
18 rivastigmine transdermal system?

19 MR. MINION: Objection to form.

20 Outside the scope of the 30(b) (6) notice.

21 THE WITNESS: I have not seen these
22 data.

23 (End of testimony)

24 Q. What's your current job title there?

1 A. I'm heading the project management
2 department in LTS.

3 Q. And when did you start in that position?
4 Sorry.

5 A. I started with LTS in November 1997. The
6 Exelon patch was the first project which I took
7 responsibility for when I started at LTS.

8 Q. You don't have any independent knowledge
9 of the testing aside from the documents?

10 A. I was not at LTS at this time, so I just
11 know what I know from reading the documents.

12 Q. Let's start with that. So after they
13 confirmed that they believed the degradation was
14 oxidative in nature, what was the next step?

15 A. After they had identified the structure of
16 the two degradation products and the possible
17 pathways, they started to look into ways on how
18 to reduce the amount of degradation.

19 Q. In what ways did they evaluate?

20 A. Based upon the information I'm aware of,
21 since they knew it was oxidative degradation
22 based upon the data, they tested antioxidants in
23 order to find out whether that would have an
24 impact on the formation of the degradation

1 products.

2 Q. Which antioxidants did they test?

3 A. Based upon the data I had access to, they
4 tested tocopherol, ascorbyl palmitate, and the
5 combination of both.

6 Q. So you're not aware of any other
7 antioxidants?

8 A. I'm not.

9 Q. Why did the working group believe that
10 these antioxidants would reduce the amount of
11 degradation?

12 MR. MINION: Objection to form.

13 THE WITNESS: I think there was no
14 -- I would use another word. I think there was
15 no belief. They were just making trials in order
16 to find out whether antioxidant would be able to
17 reduce the level of degradation which was
18 observed.

19 Q. What were the results of the testing of
20 the tocopherol and the ascorbyl palmitate?

21 A. Astonishingly and unexpectedly, it turned
22 out that the vitamin E was having the best impact
23 on the formation of the degradation products.

24 Q. So you're saying it was astonishing that

1 an antioxidant would prevent oxidation?

2 A. It's astonishingly because you can't
3 predict which kind -- whether an antioxidant --
4 it's not predictable. You may be successful.

5 You may not be successful. And it's not
6 predictable which kind of antioxidant is working.

7 Q. So it's not predictable that an
8 antioxidant stops oxidation?

9 MR. MINION: Objection to form.

10 A. It's not predictable that any kind of
11 antioxidant is stopping any kind of oxidation.

12 Q. So you're saying it's entirely
13 unpredictable that you have no way of knowing
14 whether or not an antioxidant could stop
15 oxidation?

16 MR. MINION: Objection to the form.

17 Outside the scope of the 30(b) (6) notice.

18 THE WITNESS: That's not what I'm
19 saying, what I'm saying is it's unpredictable in
20 respect to a specific API -- specific formulation
21 which antioxidant is going to work. You can't
22 predict. You have to run a series of experiments
23 in order to find out whether at all and which one
24 is doing the job.

1 Q. To reduce the degradation of rivastigmine,
2 you'd have to select an antioxidant that was
3 effective with respect to rivastigmine; right?

4 MR. MINION: Objection to form.

5 THE WITNESS: That's not correct.

6 What I'm saying it must be effective for the API
7 in combination of the formulation, the API is
8 composed in.

9 Q. So you're saying that not every
10 antioxidant would be effective with respect to
11 rivastigmine in a transdermal system; right?

12 MR. MINION: Objection to form.

13 Outside the scope of the 30(b) (6) witness.

14 THE WITNESS: What I'm saying, it's
15 not predictable which antioxidant would work and
16 would result in reduction of the amount of
17 degradation products observed.

18 (End of testimony).

19 MR. FINEMAN: Your Honor, I believe
20 we worked everything out. We need a couple of
21 minutes for technical purposes.

22 THE COURT: All right.

23 MR. FINEMAN: In the meantime, it
24 will give me an opportunity to clear up my under-

1 seal document issue. I consulted with Mr. McCann
2 while we were talking about the video clips as
3 well, so the record is clear, Your Honor, it is
4 JTX 65, JTX 177, and JTX 200 that should be
5 placed under seal. And of those three, JTX 177
6 is the DMF that we would coordinate with Novartis
7 to make sure Your Honor has a copy.

8 THE COURT: All right. Then those
9 three documents are under seal.

10 MR. FINEMAN: Thank you, Your Honor.

11 THE COURT: All right. So are you
12 working on getting this next video ready?

13 MR. FINEMAN: Yes, I think it should
14 only be a minute.

15 THE COURT: By the way, the last
16 deposition witness who I assume is Mr. Theobald,
17 does he have a first name?

18 MR. FINEMAN: I believe it's Frank,
19 Your Honor.

20 THE COURT: All right:

21 (Deposition testimony).

22 THE WITNESS: My name is Joerg
23 Ogorka. I'm living in Germany. The street name
24 is Im Steinbrunnen -- sorry, 19/3, 79585 Steinen

1 in Germany.

2 Q. Would you consider adding an antioxidant
3 to prevent oxidation to be a common-sense
4 solution?

5 A. You're talking in general terms or do you
6 talk about the Exelon patch?

7 Q. Let's talk about in general terms first.

8 A. In general terms, considering to prevent
9 or slow down oxidation by means of an antioxidant
10 is something which you may consider. What is
11 uncertain, though, is how to prevent. There are
12 -- depending on what the situation is, you may
13 exclude oxygen, for example. You cannot predict
14 which antioxidant will be effective. That is
15 very much compound-specific and chemistry related
16 to the compound and also how the antioxidant
17 works. There is some chemical interaction that
18 is not predictable.

19 So it's not something -- it's not an
20 obvious solution you can offer right away. There
21 requires a lot of experimentation to identify the
22 right antioxidant and even more experimentation
23 to establish the adequate level of this.

24 Q. As a general matter, though, adding an

1 antioxidant to prevent or minimize oxidation
2 would be something that would be common sense to
3 attempt; is that right?

4 MR. MINION: Objection to form.

5 THE WITNESS: There are many ways to
6 address instability and degradation. So --

7 Q. I want to be clear. I'm talking about
8 oxidation. So not --

9 A. I'm talking also there -- I guess you may
10 want to look into other ways, for example,
11 excluding oxygen, as an option. If you know any
12 -- any excipient could do any oxidation, might
13 exclude this one.

14 But, yes, using antioxidant is one
15 of the means one could consider once you have
16 established the mechanism and know it's
17 oxidation, which is not obvious right away. It
18 requires a lot of experimentation, structure
19 elucidation and chemical know-how to understand
20 is this an oxidative pathway that led to the
21 degradation perhaps or is this anything else.

22 Q. Which antioxidants are you aware of that
23 LTS or Sandoz tested in the Exelon patch?

24 A. I'm aware of tocopherol and ascorbyl

1 palmitate.

2 Q. Would you agree that they had been used in
3 pharmaceutical formulations prior to 1995?

4 A. As I said, I don't know other examples. I
5 just think it has been known before, yeah; but I
6 don't have examples.

7 But what was not known, maybe if I
8 just add this, is that the tocopherol did a much
9 better job as antioxidant than the ascorbyl
10 palmitate. That was clearly unobvious. Because
11 if you would have guessed prior, you would have
12 thought it might be the other way around.

13 Q. You're saying that it's unobvious that an
14 antioxidant would stop oxidation?

15 A. No, it was unobvious to see how good the
16 effect was, in terms of effectiveness. You could
17 see that the effectiveness of this tocopherol was
18 much better than the one of ascorbyl palmitate.
19 And the effectiveness meaning the level of
20 resulting degradation products out of Exelon over
21 time, this was unpredictable. That required the
22 experiments to be made to then establish this.

23 Q. So it was unpredictable that tocopherol
24 reduced the amount of oxidation?

1 A. First of all, it's unpredictable whether
2 or not it would reduce the amount of degradation
3 products from Exelon. This is unpredictable as
4 you can see as it was unpredictable that the
5 ascorbyl palmitate was not a good antioxidant.
6 That's why I say it is unpredictable which one
7 would work. That's why a series of different
8 options were tried. And the clear
9 differentiation of tocopherol being superior to
10 others, that was unpredictable.

11 Q. So you're saying that it was unpredictable
12 that when you tested tocopherol and ascorbyl
13 palmitate, tocopherol worked better than ascorbyl
14 palmitate?

15 A. As an antioxidant, yes.

16 Q. You've just been handed a document marked
17 as Exhibit 1. And if you look at the bottom
18 right corner, it's bearing Bates number LTS
19 0055040 through LTS 0055063. This document
20 appears to be a fax and attachment from yourself
21 to Paul Gargiulo. The subject is ENA TDS market
22 formulation development report. Did I read that
23 correctly?

24 THE WITNESS: You have

1 Q. So you're saying now while your company is
2 in litigation asserting patents that require an
3 antioxidant, that all of a sudden it has to be a
4 suitable antioxidant; is that right?

5 A. I don't think that you say all of a sudden
6 it has to be. I mean, it has been there all the
7 time, as you see when you look at the data of the
8 document. You see the huge difference of the
9 unsuitability -- the suitability of tocopherol
10 and the unsuitability of ascorbyl palmitate, these
11 data are there. It's not a new statement from my
12 perspective. It's just -- as we discussed this,
13 is clearly showing that the data speak for
14 themselves, so to speak, that you cannot just
15 take any antioxidant and then have solved the
16 problem.

17 Q. Is ascorbyl palmitate a suitable
18 antioxidant for rivastigmine?

19 A. Ascorbyl palmitate looks like not to be
20 suitable for the purpose.

21 Q. So not an antioxidant that you would test
22 would necessarily be suitable for rivastigmine;
23 right?

24 A. That is true, what you're saying, not any

1 antioxidant you would select or test would give
2 you a suitable antioxidant for Exelon patch.

3 Q. But knowing that the Exelon patch was
4 subject to oxidation, here you could assume that
5 the addition of antioxidants would reduce that
6 degradation?

7 MR. MINION: Objection to form.

8 A. That was a driving rationale for testing
9 there.

10 Q. But then the testing would determine
11 whether or not the antioxidant actually worked;
12 is that right?

13 A. The testing would show which one is the
14 one, and what is the effect of this antioxidant
15 in terms of, in terms of reducing the speed of
16 oxidation, yeah.

17 Q. And would you agree that it was reasonable
18 to assume that tocopherol or ascorbyl palmitate
19 may reduce the degradation --

20 MR. MINION: Objection to form.

21 Q. -- in the transdermal patch?

22 MR. MINION: Objection to form.

23 THE WITNESS: That was -- that was
24 the hypothesis that some of these antioxidants

1 that we tested would work, and of course any hope
2 that you put into your work saying hopefully one
3 of these candidates I'm putting in there will in
4 the end prove.

5 MR. BROWN: So, Your Honor, we're
6 finished with the deposition clips. Our next
7 witness will be Dr. Graham Buckton. We think,
8 given the time, it's probably appropriate to
9 start tomorrow morning.

10 THE COURT: All right. Well, so I'm
11 just going to charge you three minutes and
12 anymore minutes I have to use up today.

13 MR. BROWN: Three minutes is fine,
14 Your Honor.

15 THE COURT: So we're done. So I can
16 see that, subject to any adjustments, if there
17 are any, you're very close to both having used
18 three and a half hours. You'll get the exact
19 time tomorrow morning.

20 Just in terms of -- so, we have Dr.
21 Buckton. We have some other expert whose resume
22 I haven't seen for your side and then we have
23 Dr. Klibanov. And that's kind of what we're
24 expecting for tomorrow; right?

1 MR. BROWN: Correct, that I believe,
2 is the rest of the case, Your Honor.

3 MR. KALLAS: Your Honor, they're
4 bringing Dr. Buckton on two issues,
5 noninfringement and I assume they're bringing him
6 back after the experts you haven't seen the CV of
7 after that, to do the 112 issues. Then we'll
8 have Dr. Klibanov.

9 THE COURT: Can't we do the
10 noninfringement all at once?

11 MR. KALLAS: Well, we can if he
12 separate them. If you recall from the pretrial
13 order, their infringement case has blurred with
14 their 112 case. And we're at a loss. It's a
15 moving target and we're at a loss as what is 112.

16 THE COURT: I ruled at the pretrial
17 they have to finish infringement before they can
18 start on --

19 MR. KALLAS: The Pretrial Order
20 specifically says infringement should finish and
21 then you start invalidity. That's our
22 preference.

23 I know I don't want to inconvenience
24 the witness. He's going to be here.

1 THE COURT: No. No. I'm not too
2 worried. He gets paid well for his
3 inconvenience.

4 Is that what you're planning on
5 doing, Mr. Martin -- sorry, Mr. Brown?

6 MR. BROWN: We were planning to
7 bring him one time and have him take the stand
8 and testify. I think that's the normal course of
9 things. We're happy to do it however the court
10 wants us to do it.

11 MR. KALLAS: Your Honor, our problem
12 is, as we said at the pretrial conference,
13 they're blurring the issues. You then said you
14 would allow Dr. Klibanov to handle it, whatever
15 they came forward with.

16 But unless we know what's
17 infringement and 112.

18 THE COURT: So, Mr. Brown seems to
19 be agreeable. So Dr. Buckton, if he's the first
20 witness tomorrow, will testify on
21 noninfringement. They can cross-examine on
22 noninfringement. You can rest your
23 noninfringement case and then you can proceed
24 with your invalidity case and call whichever one

1 you want.

2 And you can call them, you know.

3 You can rest and start over again with him or you
4 can call your other expert. Right?

5 MR. BROWN: That's fine, Your Honor.

6 THE COURT: All right. So, as a
7 practical matter, do we think this is going to
8 take another seven hours tomorrow?

9 MR. KALLAS: They're all his
10 witnesses except for Dr. Klibanov, you know.

11 THE COURT: You say they're all his
12 witnesses. He has two. You have one; right?

13 MR. KALLAS: Well, put it this way,
14 he has the majority of -- I misspoke, Your Honor.
15 He has the majority of witnesses.

16 Depending on how much they do with
17 112 is how much Dr. Klibanov will have to
18 respond. I can't imagine Dr. Klibanov's more
19 than 45 minutes. But, again, I don't know what
20 their actual plan is.

21 THE COURT: All right. Is there
22 anything else you want me to address tonight
23 or tomorrow morning? Well, I guess you can't
24 tell me what you want me to address tomorrow

1 morning.

2 Is there anything you want me to
3 address tonight?

4 MR. FINEMAN: I'd just like to hand
5 up Dr. Michniak-Kohn's CV.

6 THE COURT: Oh, okay. Thank you.

7 All right. Did I give you back the
8 other two that you had handed up earlier or, I
9 mean, I looked at them and I'll give them back,
10 so we don't have extra copies floating around. I
11 will look at Dr. Michniak-Kohn's overnight.

12 Anything else before -- so, do you
13 want me to come out tomorrow morning sometime
14 before we actually start to see whether you have
15 any problems or --

16 MR. BROWN: I think that's probably
17 a good idea like today, Your Honor.

18 THE COURT: Well, and did you have a
19 little trouble getting in the courthouse this
20 morning?

21 MR. FINEMAN: Pretty smooth, Your
22 Honor.

23 THE COURT: Oh, do we --

24 (Following a discussion held off the

1 record:)

2 THE COURT: Okay. So I think -- all
3 right. Well, so I'll plan to sort of just come
4 out and see what's happening with you all at 8:00
5 tomorrow. We'll start at 8:30.

6 And if we need to discuss things
7 between 8:00 and 8:30, that's on my time, not
8 yours. Okay?

9 MR. BROWN: Thank you, Your Honor
10 list.

11 THE COURT: All right. So I'll see
12 you tomorrow, then.

13 THE CLERK: All rise.

14 (Court was recessed at 5:02 p.m.)

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1 State of Delaware)
2)
New Castle County)

3 CERTIFICATE OF REPORTER

I, Heather M. Triozzi, Certified Professional Reporter, Registered Professional Reporter and Notary Public in the State of Delaware, do hereby certify that the foregoing record, Pages 1 to 346 inclusive, is a true and accurate transcription of the above-captioned proceeding on the 1st day of May, 2014, in Wilmington.

9 IN WITNESS WHEREOF, this 1st day of
May, 2014, at Wilmington.

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16 DATED: May 1, 2014

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